Apathy in schizophrenia as a deficit in effort-based decision-making and option generation

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Contents

Abstract

Schizophrenia is one of the most debilitating psychiatric disorders. Patients often suffer from a pronounced reduction in goal-directed behavior (i.e., apathy). Apathy is a very persistent and treatment-resistant symptom that is closely linked to the patients' functional outcome and life satisfaction. Despite its undisputed major impact on the lives of affected people and society, little is known about mechanisms underlying apathy in schizophrenia.

Schizophrenia and other psychiatric disorders are commonly accompanied by maladaptive or deficient decision-making. Recently, decision scientists from the fields of psychology, economics, neuroscience, and medicine have started to investigate aberrations in decision-making of schizophrenia patients in search of possibly causal disease mechanisms. Generally, the decision-making process can be divided into roughly three sequential stages: (1) option generation, (2) option selection, and (3) outcome evaluation. Dysfunctions in one or more of these stages may lead to a reduction in goal-directed behavior and thus to increased apathy. While our knowledge of apathy-linked deficits in outcome evaluation (learning) is quite advanced, less is known about how apathetic patients integrate effort and reward to make a goal-directed decision (effort-based decision-making). It is possible that patients overweigh effort costs in their decision-making, which could be specifically linked to apathy severity. Moreover, the "predecisional" stage of option generation has not yet been investigated in the context of apathy in schizophrenia. The present doctoral thesis aims to contribute to the closure of these research gaps.

In the first study (chapter 2.1, appendix A), we sought to validate a newly developed effort discounting task in healthy participants. The task involved binary choices between various combinations of monetary reward and physical effort (handgrip force). We could show that participants processed both reward and effort information, and discounted reward with increasing effort. Moreover, we investigated whether a linear, hyperbolic, or parabolic model best characterizes the functional form of discounting. In our dataset, the concave parabolic model clearly outperformed the other two models on the individual and group level. The parabolic model predicts low discounting in low effort levels with an exponential increase towards the subjective maximum force level.

In the second study (chapter 2.2, appendix B), we applied a slightly adapted version of the effort discounting task developed in study 1 to test the hypothesis that apathy in schizophrenia would be associated with increased effort discounting. In fact, we found a strong and specific correlation of apathy with effort discounting, independent of other relevant clinical, demographic, and cognitive measures.

In the third study (chapter 2.3, appendix C), we applied verbal protocol analysis to assess the hypothesis that apathy is associated with impaired option generation. As hypothesized, we found a strong negative correlation of apathy with the quantity of generated options, even when controlling for confounding clinical variables such as diminished expression (which includes alogia).

From an application perspective, our effort discounting task might serve as a "behavioral readout" for apathy in the context of pharmacological or psychotherapeutic intervention studies. In view of the strong link of option generation with apathy, it is conceivable that a training of option generation in a therapeutic setting might ameliorate apathy symptoms. Future research should aim to identify specific brain-level correlates of apathy-linked decision-making abnormalities, which will hopefully pave the way for novel treatment options.

The studies described in this doctoral thesis introduce a novel effort discounting task and expand our knowledge about apathy-related decision-making deficits in the stages of option selection and option generation. In conclusion, our data, together with the existing research literature, strongly suggest that specifically apathy in schizophrenia is associated with aberrations in all stages of goal-directed decision-making, which is likely connected to the persistence and treatment-resistance of the symptom.

Zusammenfassung

Die Schizophrenie gehört zu den am stärksten beeinträchtigenden psychischen Erkrankungen. Patienten leiden häufig, nebst anderen Symptomen, unter einer ausgeprägten Reduktion zielgerichteten Verhaltens (Apathie). Apathie ist ein sehr behandlungsresistentes Symptom, das in engem Zusammenhang mit dem beruflichen und sozialen Funktionsniveau und der Lebenszufriedenheit des Patienten steht. Trotz des unbestrittenen grossen Einflusses auf das Leben der betroffenen Menschen und die Gesellschaft ist wenig über die zugrundeliegenden Mechanismen der Apathie bei Schizophrenie bekannt.

Patienten mit Schizophrenie oder anderen psychiatrischen Erkrankungen zeigen häufig dysfunktionales Entscheidungsverhalten. Wissenschaftler aus den Disziplinen Psychologie, Ökonomie, Neurowissenschaften und Medizin haben begonnen Symptome der Schizophrenie und deren Entstehung in Zusammenhang mit dem dysfunktionalen Entscheidungsverhalten zu bringen. Vereinfachend kann der Entscheidungsprozess in drei sequentielle Stufen unterteilt werden: (1) Generierung von Handlungsoptionen, (2) Optionsselektion und (3) Ergebnisevaluation. Eine Störung in einer oder mehreren Stufen kann zu einer Reduktion in zielgerichtetem Verhalten und folglich zu Apathie führen. Während unser Wissen über den Zusammenhang von Apathie mit Ergebnisevaluation (Lernen) vergleichsweise fortgeschritten ist, ist weniger bekannt über den Zusammenhang mit der Phase der Optionsselektion. Insbesondere bleibt offen, inwiefern Apathie mit einem Defizit in der Integration von Belohnung und Aufwand bei der Selektion von Optionen zusammenhängt. Es wäre möglich, dass apathische Patienten spezifisch die „Aufwandkosten" in der Optionsselektion überbewerten. Des Weiteren ist die Phase der Generierung von Handlungsoptionen noch nicht im Zusammenhang mit der Apathie bei schizophrenen Patienten untersucht worden. Die vorliegende kumulative Dissertation soll zur Schliessung dieser Forschungslücken beitragen.

In der ersten Studie (Kapitel 2.1, Anhang A) wurde ein neu entwickeltes Entscheidungsexperiment zur Erfassung von „Effort discounting" in einer gesunden Stichprobe validiert. Das Experiment beinhaltet binäre Entscheidungen zwischen verschiedenen Kombinationen von monetärer Belohnung und physischer Anstrengung

(Griffkraft gemessen mit einem Hand-Dynanometer). Wir konnten zeigen, dass die Teilnehmer sowohl Belohnungs- wie auch Aufwandaspekte in ihrem Entscheidungsverhalten integrierten und mit zunehmendem Aufwand die Belohnung stärker abwerteten. Des Weiteren wurde untersucht, ob ein lineares, hyperbolisches oder parabolisches Modell das Entscheidungsverhalten am besten erklären konnte. Das parabolische Modell konnte in unserem Datensatz auf Individuums- und Gruppenebene am meisten Varianz erklären. Das parabolische Modell zeichnet sich durch eine geringe Diskontierung im tiefen Aufwandsbereich und durch einen exponentiellen Anstieg bei der Annäherung an das subjektive Kraftmaximum aus.

In der zweiten Studie (Kapitel 2.2, Anhang B) wurde eine leicht adaptierte Version des in Studie 1 entwickelten Entscheidungsexperimentes bei einer Stichprobe von Patienten mit Schizophrenie durchgeführt. Es konnte eine starke und spezifische Korrelation zwischen Stärke der Apathie und Diskontierung von Entscheidungsoptionen aufgrund von Aufwandskosten beobachtet werden. Dieser Effekt war unabhängig von anderen klinischen, demografischen und kognitiven Variablen.

In der dritten Studie (Kapitel 2.3, Anhang C) wurde die Hypothese getestet, ob Apathie bei Patienten mit Schizophrenie mit Defiziten in der Generierung von Handlungsoptionen zusammenhängt. Es konnte gezeigt werden, dass Apathie negativ mit der Quantität von generierten Handlungsoptionen korreliert.

Das entwickelte „Effort discounting“ Entscheidungsexperiment könnte in Zukunft als „Verhaltensmarker“ für Apathie im Kontext von pharmakologischen und psychotherapeutischen Interventionsstudien eingesetzt werden. In Hinblick auf die starke Verbindung von Apathie mit der Fähigkeit zur Generierung von Handlungsoptionen ist es denkbar, dass ein Training ebendieser Fähigkeit in einem therapeutischen Setting apathische Symptome lindern könnte. Zukünftige Studien sollten diese auf Verhaltensebene beobachteten Auffälligkeiten auf Hirnebene untersuchen um weitere potentielle Behandlungsoptionen zu identifizieren.

Die im Rahmen dieser Dissertation verfassten Studien stellen ein neu entwickeltes „Effort discounting“ Entscheidungsexperiment vor und erweitern unser Wissen über Apathiebezogene Auffälligkeiten im Entscheidungsverhalten. Zusammenfassend zeigen unsere Daten, zusammen mit anderen aktuellen Studien, dass bei schizophrenen Patienten spezifisch die apathischen Symptome mit Auffälligkeiten in allen Stufen des Entscheidungsverhaltens zusammenhängen. Es ist naheliegend, dass genau diese breiten Defizite bei apathischen Schizophrenie Patienten zur Persistenz und Behandlungsresistenz der Symptomatik beitragen.

1 Introduction

1.1 Decision-making research in psychiatry

Decision-making is a complex process, relying on a multitude of psychological and neurobiological mechanisms. The endpoint of decision-making is to arrive at an optimal outcome. Consequently, intact decision-making is crucial for personal and occupational success. Aberrant or maladaptive decision-making is very common in various psychiatric disorders. Thus, it has been proposed that decision-making research might help to elucidate underlying mechanisms of these disorders, both on the behavioral and neural level (Hasler, 2012; Lee, 2013; Paulus, 2007; Rahman et al., 2001). The last decade has seen a strong increase in interdisciplinary cooperation between the “classical” decision-scientists from the fields of psychology and economics and neuroscientists, which has resulted in the novel discipline of neuroeconomics. Psychiatry has been considered being one of the most promising fields of application of neuroeconomic theory and research (Hasler, 2012; Kishida et al., 2010; Rangel et al., 2008; Sharp et al., 2012). In line with this, the present doctoral thesis aims to investigate the symptom of apathy in schizophrenia from the viewpoint of deficient decision-making.

1.2 Schizophrenia and its symptoms

Schizophrenia is a debilitating psychiatric disorder that affects approximately 1% of the population across cultures (Peraala et al., 2007), with males tending to be affected more often than females (Hafner, 2003). In many cases, schizophrenia first manifests in adolescence or young adulthood (Delisi, 1992) with a high risk for chronicity and shortened life expectancy (Carpenter and Buchanan, 1994). In addition to the burden on patients and their families, schizophrenia also poses an immense economic burden to society. In industrialized countries, schizophrenia is the most expensive psychiatric disorder, causing an estimated 1.5 – 2.5% of the total health costs (Rössler, 2011). Despite its undisputed major impact on the lives of affected people and society, research progress on underlying disease mechanisms has been slow in the last decades and consequently treatment options still remain limited (Walker et al., 2004).

The distinctive symptom pattern of schizophrenia was first described by Kraepelin (1896), who referred to it as "dementia praecox" and differentiated it from manic-depressive disorder. In 1911, Bleuler coined the term "schizophrenia", referring to disrupted thought processing and a fundamental split among thought, emotion, and behavior. He also recognized the heterogeneity of the illness and thus spoke of the "group of schizophrenias" (Bleuler, 1911). Essential progress in the conceptualization of schizophrenia was made in 1959 by Schneider, who proposed the psychotic key symptoms of hallucinations and delusions to be diagnostic for schizophrenia (Schneider, 1959). In the 1980's, clinicians and researchers started to emphasize the differentiation between "positive" and "negative" symptoms of schizophrenia (Andreasen, 1982). Positive symptoms are those that constitute an excess of experience and behavior, such as hallucinations, delusions, and disordered thought and speech. Negative symptoms, in contrast, refer to a decrease in normal emotional experience and/or behavior. They include anhedonia, asociality, avolition, lack of normal distress, blunted affect, and alogia (Kirkpatrick et al., 2011).

To achieve uniformity and diagnostic reliability, criteria for schizophrenia and other mental disorders have been described in different diagnostic systems. The most widely used system today is the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; APA, 2013). Using DSM-5, schizophrenia can be diagnosed if symptoms have been present for at least 6 months. The symptom domains for schizophrenia include: (1) hallucinations, (2) delusions, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, and (5) negative symptoms. At least two of these symptoms (at least one positive symptom) must be present for at least one month. In addition to these symptom criteria, patients must be affected in their social and occupational functioning. Moreover, mood disorders such as mania or depression, as well as medical conditions, or substance abuse that might lead to psychotic symptoms must be ruled out. Although these criteria help to group related psychiatric conditions and have aided clinical practice, patients diagnosed with schizophrenia still represent a relatively heterogeneous group. Consequently, it has been proposed that in addition to research on categorical diagnoses and group comparisons with healthy controls, it is crucial to investigate specific target symptoms in a dimensional approach (Van Os et al., 1999). This is partially recognized in the DSM-5 (APA, 2013), which includes a research appendix with assessment scales for the following eight symptom dimensions or related impairments in schizophrenia: (1) hallucinations, (2) delusions, (3) disorganized speech, (4) abnormal psychomotor behavior, (5) impaired cognition, (6) depression, (7) mania, and (8) negative symptoms (see Figure 1). These dimensions themselves can be split-up into additional sub-dimensions. Negative symptoms, for instance, are increasingly recognized as consisting of two dissociable factors: diminished expression and apathy[1] (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Malaspina et al., 2014; Messinger et al., 2011; Strauss et al., 2012). Apathy has been linked to poor functional outcome (Faerden et al., 2009; Fervaha et al., 2014; Fervaha et al., 2013c; Strauss et al., 2013) and low life satisfaction (Evensen et al., 2012; Fervaha et al., 2013a; Packer et al., 1997). Moreover, treatment responsiveness of apathy symptoms to current pharmacological therapies is negligible (Erhart et al., 2006). Thus, apathy constitutes one of the most important target symptoms in schizophrenia, both for research and future development of efficacious treatment options.

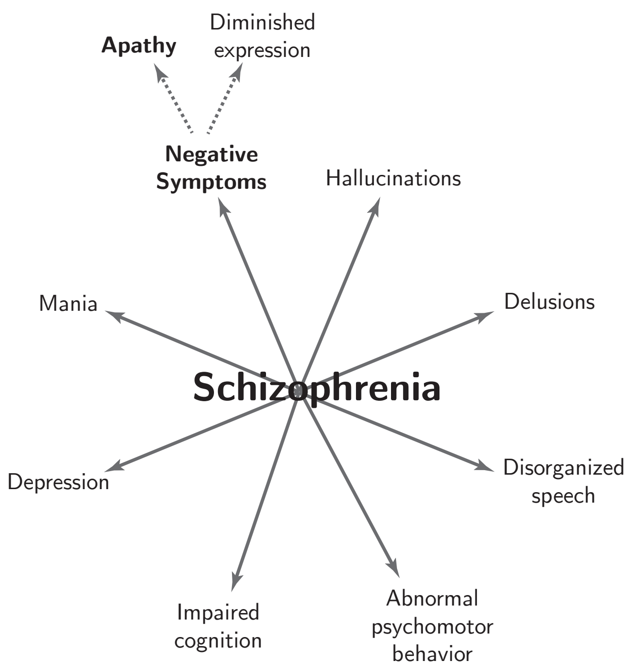

Figure 1. Symptom dimensions and related impairments of schizophrenia in the DSM-5 research appendix (APA, 2013).

[1] Please note that the terms "apathy", "amotivation", and "avolition" are used interchangeably in the current literature.

1.3 Apathy-related impairments in goal-directed decision-making?

Aberrant and dysfunctional decision-making is commonly observed in neuropsychiatric disorders, including in apathetic states of schizophrenia (Lee, 2013; Paulus, 2007; Rahman et al., 2001). Goal-directed decision-making has been conceptualized as consisting of different stages or computations (Kalis et al., 2008; Rangel et al., 2008; Rangel and Hare, 2010; Sinha et al., 2013): (1) option generation, (2) option selection, and (3) outcome evaluation (see Figure 2). Please note that this sequential conceptualization is highly schematic. In reality, these processes might run in parallel and might be differentially involved in different contexts.

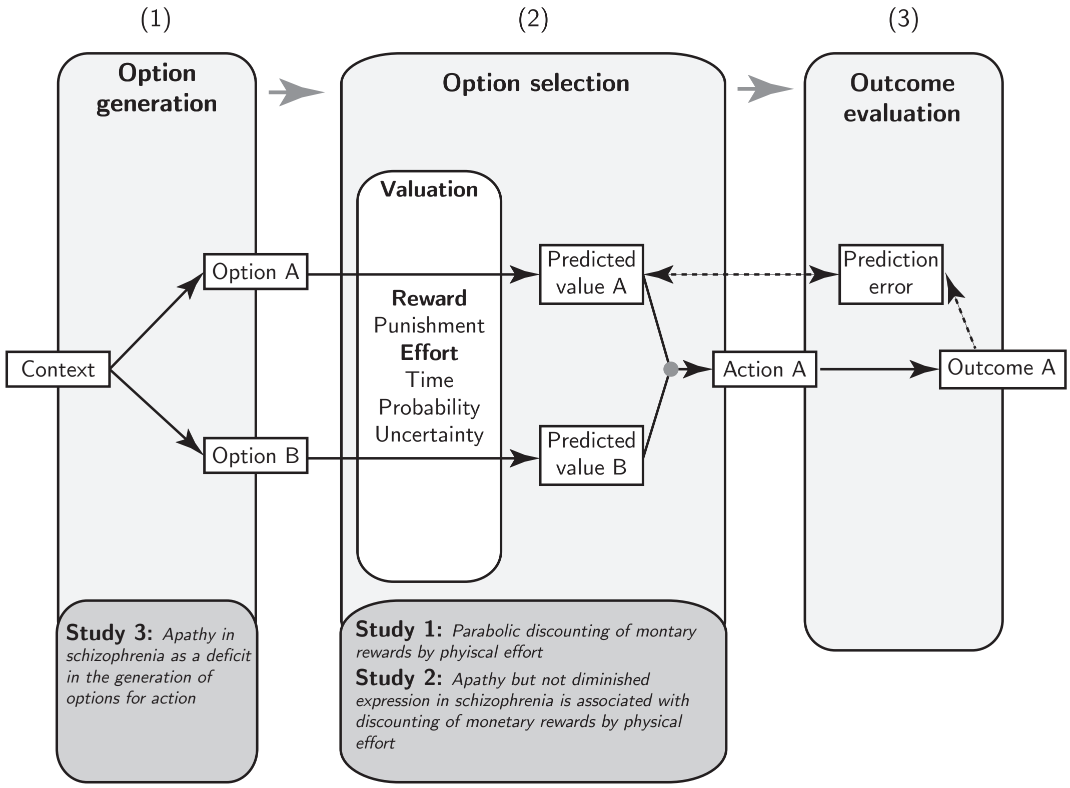

Figure 2. Conceptual framework of goal-directed decision-making (adapted from Kalis et al., 2008; Sinha et al., 2013). The studies presented in this thesis can be assigned to the stage of option selection (Study 1 & 2) and option generation (Study 3).

The three stages (1-3) can be thought of in the following way. **(1)** In ill-structured real-world scenarios, options (e.g., for action) in a given context (set of external and internal states) have to be generated first. This stage has been somewhat neglected by traditional models of decision-making (e.g., Ernst and Paulus, 2005; Heckhausen, 1991) and thus most research has focused on option selection using experimental paradigms with options already at hand. **(2)** In the option selection stage, following option generation, valuation and subsequent selection of generated options takes place. Goal-directed choice requires the computation of *stimulus values* (i.e., the value of the predicted outcome of each action) and *action costs* (i.e., the predicted cost associated with each action), which are then integrated into predicted *action values* (see equation below; adapted from Rangel and Hare, 2010). Both stimulus value and action cost are weighted according to temporal delay and probability at which they are expected to occur (β_1 & β_2 in the equation below integrate delay and probability costs for stimulus value and action cost, respectively). This has been termed delay or probability "discounting" (Rachlin, 2006). In analogy, the devaluation of the stimulus value due to action costs, such as the physical effort required to attain the rewarding outcome, has been referred to as "effort discounting" (Botvinick et al., 2009).

$$Action\ Value = \ \beta_1 * Stimulus\ Value - \ \beta_2\ * Action\ Cost$$

In order to make an optimal choice, the computed value of different actions then have to be compared. The conversion of action values to choice is stochastic (leading to action probabilities) and follows a soft-max or logistic function (Rangel and Hare, 2010). If the chosen action is implemented, an outcome value results that possibly deviates from the predicted action value (also see *predicted utility* vs. *experienced utility* as discussed by Kahneman et al., 1997). **(3)** Thus, in a last stage, the outcome value is compared to the predicted outcome and the resulting "prediction error" is used to update the action (and stimulus) value for future decisions (learning). The intactness of these three stages of goal-directed decision-making is crucial for the maintenance of purposeful behavior and goal striving and thus for personal and occupational success. By contrast, dysfunctions in one or more of these stages might lead to observed apathy (i.e., a quantitative reduction in goal-directed behavior; Levy and Dubois, 2006) in patients with schizophrenia as outlined below.

An increasing number of studies have investigated apathy-related alterations in decision-making, aiming at elucidating potential causal disease mechanisms (and neural correlates as assessed with modern imaging methods). Learning from outcomes (outcome evaluation; Figure 2) has repeatedly been shown to be impaired in apathetic schizophrenia patients (Murray et al., 2008; Strauss et al., 2011; Waltz et al., 2007; Waltz and Gold, 2007). The rationale behind this link is that if patients fail to connect rewarding outcomes to the preceding action ("Go-learning"), they might also fail to initiate goal-directed action to attain the outcome in the future, which could result in increased apathy. In contrast to deficient reward learning, there is evidence of relatively intact punishment learning ("NoGo-learning") in apathetic schizophrenia patients (Strauss et al., 2011; Waltz et al., 2007; Waltz et al., 2011). In the stage of option selection, as described above (see Figure 2), one has to differentiate between valuation of a stimulus (e.g., how rewarding is a potential peace of cake?) and the expected cost of the associated action (e.g., how effortful is the walk to the pastry shop?), which are then integrated into action values. There is substantive evidence for a deficit in the valuation of potential reward (Barch and Dowd, 2010; Dowd and Barch, 2010; Gard et al., 2007; Gold et al., 2008; Kring and Barch, 2014). However, our knowledge is rather limited when it comes to the question whether and how valuation of action costs is associated with apathy. It is conceivable that apathetic patients might specifically overweigh action costs such as physical effort, which might explain the observed reduction in goal-directed behavior. In addition to deficient option selection, apathy might also be linked to deficits in the stage of option generation (see Figure 2). Possibly, patients might fail to generate a sufficient quantity or quality of options for action, which could be specifically linked to apathy severity. The present thesis aims to provide new insights about these two open questions.

1.4 Research objectives

(1) The first study (chapter 2.1 & appendix A) reports a newly developed binary choice paradigm that assesses how physical effort (handgrip force) devalues monetary rewards (effort discounting) in a sample of healthy participants. In other words, this task aims to measure how strongly the action cost of physical effort discounts the stimulus value of monetary reward, reflected in a reduced action value that we infer from the individuals' revealed preference in binary choice (see equation chapter 1.3). The objective of this study was twofold: first, before applying the task in a patient sample, we wanted to validate it in healthy participants. Second, we aimed to investigate the functional form of effort discounting in a task with constant physical force and monetary rewards. Studies on other forms of discounting, such as delay discounting, have mainly reported exponential or hyperbolic functions to best fit their data (Camerer, 1999). However, it is unclear whether this can be extended to effort discounting, or if some other function better characterizes the discounting of monetary rewards by physical effort.

(2) In the second study (chapter 2.2 & appendix B), we applied a slightly adjusted form of the effort discounting task developed in study 1 in a sample of schizophrenia patients and aimed to test the hypothesis that specifically apathy would be positively correlated with the degree of effort discounting. In other words, we expected that more severe apathy symptoms would be associated with a stronger devaluation of rewards when effort is required.

(3) In the third study (chapter 2.3 & appendix C), we aimed to investigate whether apathy in schizophrenia is associated with dysfunctional option generation. More specifically, we were interested whether apathy would correlate negatively with the quantity of generated options in ill-structured real-world scenarios as assessed by verbal protocol analysis.

In the following chapter 2, the three studies of this cumulative thesis are shortly summarized and discussed. The more detailed research articles published or to be published in specialized research journals have been added as appendices.

Study 1 (Appendix A):
Hartmann, M. N., Hager, O. M., Tobler, P. N., Kaiser, S., 2013. Parabolic discounting of monetary rewards by physical effort. Behavioural Processes 100, 192-196.

Study 2 (Appendix B):
Hartmann, M. N., Hager, O. M., Reimann, A. V., Chumbley, J. R., Kirschner, M., Seifritz, E., Tobler, P. N., Kaiser, S., in press. Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort. Schizophrenia Bulletin.

Study 3 (Appendix C):
Hartmann, M. N., Kluge, A., Kalis, A., Mojzisch, A., Tobler, P. N., Kaiser. S., under review. Apathy in schizophrenia as a deficit in the generation of options for action. Journal of Abnormal Psychology.

2 Summary and Discussion of Studies

2.1 Study 1: Parabolic discounting of monetary rewards by physical effort[2]

In the first study, we could show that in our binary choice effort discounting task healthy participants processed both reward and effort information and discounted reward with increasing effort. In other words, our task proved to be suitable for assessing discounting choice behavior in the context of monetary rewards and physical effort. We then tested whether a linear, hyperbolic, or parabolic model best characterizes the functional form of discounting. In our dataset, the concave parabolic model outperformed the other two models on the level of both individual subjects and the group as a whole. The parabolic model predicts low discounting in low effort levels with an exponential increase towards the subjective maximum force.

How humans perceive physical effort (perceived exertion) as assessed by psychometric rating scales or "online" self-reports has been reported in the classical psychophysics literature throughout the last decades (Borg, 1982; Jones, 1986; Lewis, 1965; Stevens and Mack, 1959; Stevens, 1957). These contributions all share the premise of the very intuitive *law of less work* (Hull, 1943), according to which humans and other animals will choose the easier (less effortful) option if presented with a choice between two behavioral sequences that result in the same reward.[3] Some authors have proposed non-linear power functions in order to relate effort exertion to effort perception (*Steven's power law*; Stevens and Mack, 1959). In contrast to what one would expect from this, recent studies using choice experiments to investigate effort discounting have mainly reported hyperbolic models to best relate effort to subjective value (Mitchell, 1999, 2003, 2004; Prevost et al., 2010; Sugiwaka and Okouchi, 2004). However, in these experiments effort costs were partially confounded by time costs, which have predominantly been shown to discount rewards hyperbolically (Mazur, 1987; Rachlin, 2006), and which could explain why these authors also found hyperbolic discount patterns in their experiments.

[2] Please see appendix A for full-length research paper.

[3] Note that in some situations effort might also have rewarding properties (e.g., Kim and Labroo, 2011; Kivetz, 2003).

The present results are in line with *Steven's power law* (Stevens and Mack, 1959), best characterizing the choice data with a quadratic power function, which results in a concave parabola when relating effort to action value. This expands an established psychophysical law to value-based decision-making. Our finding of a concave effort discount function has been replicated in a very recent study by Klein-Flügge et al. (in preparation), who used a more refined experimental paradigm, which enabled them to fit even more complex models to their data. More precisely, they report a two-parameter inverse sigmoidal model, which is initially concave and converges to zero for unattainable efforts. However, it is of question whether a more complex and time consuming task as used by Klein-Flügge et al. (in preparation) is feasible to apply in psychiatric patient populations, because patients might not be able to concentrate for a longer time period or fail to understand the task instructions. We conclude that in patient studies, a task with a minimum number of reward and effort levels is the preferred choice and that for the resulting, limited number of data points, our parabolic model might be sufficient for patient characterization.

Considering the results of this first study, a likely expected outcome in schizophrenia patients would be that apathy would correlate with the discount parameter (k) of the parabolic model, which modulates steepness. However, patients might also show a distinctly different form of discounting. The parabola is characterized by low discount rates in low effort levels. However, apathy in schizophrenia might be associated with changes in the discount rate particularly in these low effort levels (i.e., overweighing of low effort). This might cause the overall discount function to approach a linear pattern.

In sum, the first study of the present thesis introduces a novel binary choice paradigm and proposes that a concave parabolic model best explains effort discounting.

2.2 Study 2: Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort[4]

In the second study, we aimed to test the hypothesis that apathy in schizophrenia would be correlated with how strongly physical effort impacts value-based decision-making. We used a slightly adapted version of the effort discounting task developed in the first study and found that apathy but not diminished expression was strongly associated with the strength of discounting of monetary rewards by physical effort. Importantly, we could show that this effect is not driven by antipsychotic medication, cognition, or other relevant demographic and clinical variables. Moreover, our data suggest that it might be both the "overweighing" of effort costs and also partially the "underweighing" of reward value that leads to decisions not to engage in effortful but rewarding behavior in apathetic patients. The latter finding is in line with a growing body of research demonstrating that apathy in schizophrenia is linked to degraded reward value representations (Gold et al., 2012; Gold et al., 2008) or deficits in anticipating reward (Dowd and Barch, 2012; Esslinger et al., 2012; Grimm et al., 2012; Juckel et al., 2006; Simon et al., 2010). During the course of this doctoral thesis, several papers have been published supporting our conclusion of dysfunctional effort computation in schizophrenia (Barch et al., 2014; Fervaha et al., 2013c; Gold et al., 2013; Wolf et al., 2014). The earlier two studies by Gold et al. (2013) and Fervaha et al. (2013c) report dysfunctional effort-based choice in schizophrenia patients compared to healthy controls. However, they failed to show the critical symptom-level link with apathy in patients. Barch et al. (2014) and Wolf et al. (2014) partially found correlations of effort-based choice with symptoms. These were, however, not as specific and strong as in our study. The task used in our study differs from the tasks in the above-mentioned studies in a few critical points that might explain partial discrepancies. First and most importantly, all of these tasks operationalized effort as varying amounts of key presses executed on a computer device. In contrast, we used different physical force levels applied on a handgrip for a constant time period. This controls

[4] Please see appendix B for full-length research paper.

for time costs, whereas different amounts of button presses are strongly confounded by time. Moreover, compared to button presses, pure physical force application might tap more strongly into a motivational core process. Button presses, on the other hand, might be more closely linked to personality traits such as persistence (Cloninger et al., 1993).

The majority of the recent studies (Barch et al., 2014; Fervaha et al., 2013c; Gold et al., 2013) also manipulated probability costs (risk), which has likely led to increased cognitive demand during the task and thus possibly added noise to choice data due to cognitive deficits, which have been repeatedly reported in schizophrenia (Dibben et al., 2009; Heinrichs and Zakzanis, 1998; Keefe et al., 2006). In fact, Gold et al. (2013) and Fervaha et al. (2013c) both found positive correlations between cognitive ability and effort-based choice (better cognition was associated with less discounting), whereas in our study no significant relation arose. This suggests that our task was comprehensible to all patients, independent of their cognitive ability. Importantly, Wolf et al. (2014) additionally assessed ventral striatal reactivity in functional magnetic resonance imaging (fMRI) during a monetary guessing paradigm. This reflects an indirect measure of reactivity to rewards that is not dependent on patients' self-report. They report a significant correlation of activity in the ventral striatum with effort-based choice in patients. In other words, they found that a stronger brain response to reward is associated with an increased probability of choosing to exert effort. This replicates our finding that self-reported reward valuation in patients impacts effort-based choice in the same way. In sum, these publications represent a very strong degree of replication, highlight the advantage of physical effort, and together with our results suggest that dysfunctional effort-based decision-making might be at the core of apathy in schizophrenia.

In study 2, we used the task developed in study 1 (chapter 2.1). However, the proposed concave parabolic shape of discounting was not unequivocally observed (see Figure 3C in appendix B). The healthy control group showed a slightly concave discount curve with its characteristic slow rate of discounting in lower effort levels. In contrast, the overall patient group rather displayed a linear pattern of discounting. Because no single discount model appeared to hold for both groups, we decided to use the area under the curve over all effort levels as main dependent variable. This approach is entirely driven by data and has been shown to have comparable sensitivity as classical one-parameter discount models (Myerson et al., 2001).

Until today, there is no direct evidence for a neural substrate of dysfunctional effort computation in schizophrenia. There is, however, converging evidence from the preclinical and human neuroscience literature that can be linked to known neural abnormalities in schizophrenia (Fervaha et al., 2013b; Kring and Barch, 2014; Strauss et al., 2014). With regard to the neurochemical basis of effort computation, dopamine (DA) has been shown to play a key role in rodent and in human studies (Assadi et al., 2009; Kurniawan et al., 2011; Salamone et al., 2009). It is also well documented that schizophrenia is associated with DA abnormalities. However, the direct link from basic neuroscience literature to known deficits in schizophrenia is hard to establish. Regarding the neural circuitry of effort-value computation, fMRI data from healthy human participants (Croxson et al., 2009; Kurniawan et al., 2010; Prevost et al., 2010) suggest that effort-value computation is crucially dependent on cortico-striatal interactions, highlighting the role of the anterior cingulate cortex (ACC) and the nucleus accumbens (NAcc). This is largely in line with circuits that have been proposed to underlie apathy in neuropsychiatric disorders, including schizophrenia (Barch and Dowd, 2010; Brown and Pluck, 2000; Cummings, 1993; Levy and Dubois, 2006). In short, we have increasing knowledge from basic neuroscience on effort-cost computation, which is partially consistent with abnormalities reported in schizophrenia. However, studies that directly investigate the neural basis of effort-cost computation in schizophrenia are urgently needed to test hypotheses that are being generated from basic neuroscience.

In sum, apathy in schizophrenia seems to be linked to not only degraded reward valuation, but also to an overweighing of effort costs in value-based choice.

2.3 Study 3: Apathy in schizophrenia as a deficit in the generation of options for action[5]

In the third study, we aimed to explore whether apathy symptoms in schizophrenia are associated with deficits in the generation of options for action in ill-structured everyday

[5] Please see appendix C for full-length research paper.

scenarios. In general, we reasoned that a quantitative reduction of options in ill-structured scenarios is most likely linked to suboptimal outcomes and consequently decreased goal-directed behavior. In line with this, we found a strong correlation of apathy in schizophrenia patients with the quantity of generated options assessed by verbal protocol analysis, independent of other relevant clinical, demographic and cognitive variables.

There are two main ways of interpreting and embedding this finding into the existing literature. First, dysfunctional option generation in apathy might reflect a specific cognitive deficit. In other words, patients might fail to generate sufficient options because of impaired cognitive ability. It is well established that schizophrenia patients often suffer from a wide array of cognitive deficits (Dibben et al., 2009; Heinrichs and Zakzanis, 1998; Keefe et al., 2006). These are, however, only modestly linked to apathy symptoms, which stands in contrast to the strong negative correlation that we found with the quantity of generated options in our study (r = -0.68). This discrepancy might be explained by the fact that most studies use relatively abstract standard cognitive test batteries that are not directly linked to everyday decision-making and goal-directed behavior. The argument of the present findings reflecting a cognitive deficit is consistent with widely documented apathy-related prefrontal cortex (PFC) dysfunction in schizophrenia (Fischer et al., 2012); PFC being a brain structure strongly involved in cognition (Stuss and Knight, 2013). A second line of argument links the observed quantitative reduction in option generation to motivational deficits or deficits in cost-benefit decision-making, which has also been found in the second study of this thesis. Under the premise that the cognitive effort required to generate options for action is "costly" (Kool et al., 2010), options are generated up to the point where the anticipated effort associated with the generation of additional options outweighs anticipated benefits (Gigerenzer and Todd, 1999). Thus, the quantitative reduction of generated options in apathy might also be explained by an overweighing of cognitive effort costs. Importantly, both lines of argument –dysfunctional option generation as a cognitive vs. a motivational deficit– are not mutually exclusive; in fact, it seems most plausible that apathy-linked option generation deficits are caused by both cognitive and motivational deficits (overweighing of cognitive effort costs).

In sum, apathy in schizophrenia seems to be also associated with “predecisional” deficits. More specifically, we found strong evidence linking apathy to a reduced quantity of generated options in ill-structured real-world scenarios.

3 General Discussion

3.1 A decision-making framework for understanding apathy in schizophrenia

Apathy in schizophrenia can be conceptualized as a deficit in goal-directed decision-making. Goal-directed decision-making has been proposed to consist of three stages or computations: (1) option generation, (2) option selection, and (3) outcome evaluation. As outlined in the Introduction, if any or a combination of these computations are impaired, an increase in apathy might be observed in the affected individual. The present thesis aimed to investigate apathy-related aberrations in option selection and option generation. More precisely, the conducted experiments sought to find correlates of apathy with effort discounting and with the quantity of generated options in ill-structured real-world scenarios.

The results of the experiments support the general notion of apathy-related deficits in decision-making. First, we found very specific associations of apathy symptoms with the degree of discounting in our effort discounting task. This adds to a growing body of research demonstrating apathy-related deficits in option selection. Second, apathy symptoms were also strongly linked to option generation quantity. To my knowledge, study 3 of the present thesis is the first to empirically demonstrate such a link between apathy and predecisional deficits empirically. In sum, our data, together with the existing literature, suggest that apathy in schizophrenia is associated with deficits in all stages of goal-directed decision-making, which is likely connected to the persistence and treatment-resistance of the symptom.

It has been proposed that the nascent field of neuroeconomics is able to take a bridging role to translate research from the basic sciences (psychology, economics, neuroscience) to the psychiatric clinic and back (Hasler, 2012; Kishida et al., 2010; Sharp et al., 2012). With its multilevel research approach of refined behavioral experiments and neuroimaging, it provides a promising toolbox to explore psychopathological variation in psychiatric patients. The present thesis constitutes an example of the application of neuroeconomic experimentation on the behavioral level to better understand a specific symptom dimension in schizophrenia. Increasing interdisciplinary cooperation between researchers from the basic sciences (including neuroeconomics) and clinical researchers was also evident in the high number of participants from different fields in the recent *First Zurich Computational Psychiatry Meeting* [6], which was co-organized by the author of this thesis. In sum, the fruitful application of neuroconomic methods in psychiatry can be expected to increase even more in years to come.

The findings presented in this thesis entail some clinical implications, which are outlined in the following chapter. The next chapter then mentions limitations in regard to the conducted studies and also lists perspectives for future research.

3.2 Clinical implications

The two studies on effort discounting (study 1 & 2) entail one indirect clinical implication: the developed effort discounting task might serve as a "behavioral readout" for apathy in the context of pharmacological or psychotherapeutic intervention studies. A primary disadvantage of current clinical measures is that they assess symptoms, such as apathy, mostly through patients' self-report, which is likely to be biased (Meyer et al., 2001; Strauss and Gold, 2012). A task like ours, could be a valid alternative to these clinical interview measures as has also been suggested by others (Fervaha et al., 2013b; Kring and Barch, 2014). Moreover, our data confirm the cross-species validity of effort-based decision-making tasks, as such tasks, have been applied to study motivational deficits in mouse models of negative symptoms of schizophrenia (e.g., Ward et al., 2012). This is crucial because it supports the use of effort discounting tasks in preclinical research (e.g., mouse studies) to test the effects of novel pharmacological compounds on "apathy".

The study on option generation in schizophrenia (study 3) revealed a strong association of apathy symptom severity with the quantity of generated options. Although our results do not allow causal interpretations, one might speculate that a training of option generation ability might ameliorate apathy symptoms in patients. For ease of application, it could be implemented in a computerized setting, where patients would practice to generate options in ill-structured scenarios that are prompted by computer software. In therapy sessions,

[6] www.computationalpsychiatry.ch

patients would then learn how to transfer the option generation training to everyday life under the guidance of a trained psychotherapist.

3.3 Limitations and perspectives

Naturally, there are limitations that need mention in regard to the studies presented in this thesis. An overall limitation is that sample sizes in all studies were modest. However, the main conclusions that we draw from each of the studies is based on strong effect sizes, restricting this precautionary statement to secondary analyses that revealed results with smaller effect sizes. An additional limitation in the two patient studies was that the majority of the patients were stable inpatients treated at the Psychiatric University Hospital Zurich. Further studies are thus needed to replicate our findings in outpatient populations.

In the first study, we aimed to design a task that is suitable for patients regarding duration and complexity and thus restricted effort and reward manipulations to a minimum level. If the task would have included a greater range of effort and reward levels, possibly more complex models, beyond our one-parameter parabolic model, could have been tested as was done by Klein-Flügge et al. (in preparation). However, it is questionable whether a more complex and lengthy task is feasible for psychiatric patient populations as discussed above.

In the second study, the shape of discounting was not as clearly concave as the parabolic model of study 1 predicts. Healthy control participants showed a pattern that converged to a concave form, whereas patients showed an approximately linear pattern of discounting. Future studies should attempt to apply more refined experimental designs in schizophrenia to clarify possible apathy-linked discount function abnormalities, in addition to replicating our finding of apathy-dependent overall discounting. However, as mentioned above, it has to be considered that cognitive and time demands of the experiment should be held as low as possible for patient studies. Future studies should also investigate how cognitive effort is discounted in healthy controls (according to a parabolic model?), and how cognitive effort discounting relates to apathy symptoms in neuropsychiatric disorders. Moreover, future studies should investigate how reward and effort are processed and integrated on brain-level by applying imaging techniques such as fMRI. Data from such studies should also undergo dynamic causal modeling (Friston et al., 2003) to test models of neural dynamics between regions of interest, such as the ACC, NAcc, and orbitofrontal cortex. Additionally, it would be of interest to look into how pharmacological compounds (e.g., novel antipsychotics) impact patients' effort discounting on the behavioral and neural level.

A clear limitation of the third study was that our task was not suitable for the assessment of option quality. Ultimately, it is the quality and not the quantity that is critical for successful goal-directed behavior. However, despite its shortcomings, the main finding of this study will likely provoke new important research projects. Future research on option generation should thus design a task to assess the quality of options for action in ill-structured scenarios. As discussed, it should further be tested whether the training of option generation could improve apathy symptoms in affected patients.

Finally, it would be of interest to replicate the findings of the present thesis in the context of apathy in other neuropsychiatric disorders (e.g., depression and Parkinson's disease).

3.4 Conclusion

The studies conducted in the scope of this doctoral thesis expand our knowledge about possibly causal mechanisms of apathy that are reflected in symptom-linked abnormalities in goal-directed decision-making. However, despite considerable progress in the last few years, we still know little about neurobiological mechanisms of apathy in schizophrenia that would allow the development of more specific treatment interventions. In order to achieve this goal, interdisciplinary cooperation between clinicians and scientists on one hand, and scientists form different disciplines on the other hand, has to be further intensified and encouraged by universities and funding agencies. Finally, it is crucial not to loose track of the primary objective of our research, which is to better the lives of patients who are affected by schizophrenia and, at some point in the future, cure it.

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Appendix A: Paper 1

"Parabolic discounting of monetary rewards by physical effort".

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Short report

Parabolic discounting of monetary rewards by physical effort

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ABSTRACT

When humans and other animals make decisions in their natural environments prospective rewards have to be weighed against costs. It is well established that increasing costs lead to devaluation or *discounting* of reward. While our knowledge about discount functions for time and probability costs is quite advanced, little is known about how physical effort discounts reward. In the present study we compared three different models in a binary choice task in which human participants had to squeeze a handgrip to earn monetary rewards: a linear, a hyperbolic, and a parabolic model. On the group as well as the individual level, the concave parabolic model explained most variance of the choice data, thus contrasting with the typical hyperbolic discounting of reward value by delay. Research on effort discounting is not only important to basic science but also holds the potential to quantify aberrant motivational states in neuropsychiatric disorders.

1. Introduction

Every day, humans and other animals are faced with decisions about possible courses of actions that entail expected costs and benefits. The quality of this decision-making process is essential for the wellbeing of the individual and the survival of the species (Stephens and Krebs, 1986). In various neuropsychiatric disorders that are accompanied by aberrant motivational states, such cost–benefit decision-making seems to be critically impaired (Rahman et al., 2001). Consequently, understanding the psychological dynamics of weighing a reward against associated costs is of interest to basic behavioral science and also holds significant clinical implications.

We define rewards and costs as attributes of the expected outcome that lead to an increase or decrease in decision utility respectively (Kahneman et al., 1997). In this view, animals would generally strive to minimize expected effort. This idea was already stated in Hull's (1943) *law of less work*, according to which an organism will choose the low effort option when it faces two options that solely differ in amount of metabolic energy demands or work. In this context, the value of a given reward diminishes as a function of increasing cost, which has also been termed as *discounting* of the reward (Rachlin, 2006).

Several theoretical valuation models have been proposed that integrate benefits and costs. Discounting by delay and probability costs has been proposed to follow an exponential (*discounted utility model*; Samuelson, 1937) or hyperbolic model (Mazur, 1987). In a majority of empirical studies, the latter descriptive model has proven to provide a superior fit compared to the prescriptive exponential model derived from standard economic theory (Kirby, 1997; Myerson and Green, 1995; Rachlin et al., 1991).

Despite considerable knowledge about the neurobiology of effort-based decision-making and behavior from animal (e.g., Floresco et al., 2008) and human studies (e.g., Burke et al., 2013), only few studies have investigated the functional form of physical effort discounting. Phillips et al. (2007) proposed that effort costs would increase linearly, while others (Mitchell, 1999, 2003, 2004; Prévost et al., 2010; Sugiwaka and Okouchi, 2004) fitted hyperbolic models to their data. Contrary to the domain of delay discounting where exponential and hyperbolic functions are often compared, in the domain of effort discounting studies usually selected one type of model without testing whether others would provide a better fit. Here we compare three simple models (see below) in terms of their ability to explain effort discounting. Physical effort was operationalized as varying percentages of the subject-specific maximum voluntary contraction (MVC) on a hand dynamometer. Participants repeatedly chose between a *no effort/low reward* and a *high effort/high reward* option. In the latter, both physical effort (% MVC) and monetary reward magnitude were independently manipulated.

Based on reports that perceived effort in constant-force tasks increases as a power function of the target force (*Stevens' power law*; Stevens, 1957), we hypothesized that physical effort would

Abbreviations: MVC, maximum voluntary contraction; N, Newton; CHF, Swiss Francs; s, seconds; ms, milliseconds; SV, subjective value.

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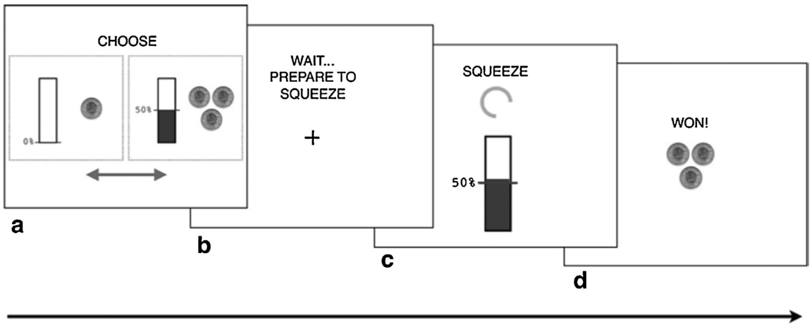


Fig. 1. Schematic of the sequence of task events. (a) Presentation of options (no time limit). (b) Fixation cross (4 s). (c) Effort exertion period (3.5 s). (d) Feedback period (3 s).

discount money as a power function. Stevens and Mack (1959) reported an exponent of 2 with ratio and magnitude production procedures on a hand dynamometer task. Thus we specifically hypothesized that we would observe parabolic (with an exponent of 2) rather than linear or hyperbolic discounting of monetary rewards by effort. These three functions crucially differ in their assumptions on how increasing force requirements impact choice: While a linear model predicts constant discounting over the whole force spectrum, the convex hyperbola predicts changes in low force to have stronger impact than changes in high force. In contrast, a concave parabolic model predicts the opposite. Consider the example of adding weight during a weight-lifting competition: The hyperbolic model predicts that adding 1 kg has a stronger impact on subjective experience at the beginning of the competition, when the lifters are well below their individual maximum. By contrast, the parabolic model predicts that the impact of adding 1 kg is larger toward the end of the competition, when lifters are close to their individual maximum and the linear model predicts the impact to be the same in both cases.

2. Materials and methods

2.1. Participants

This study's sample consisted of 24 participants (8 males) recruited from the hospital staff (Zurich University Hospital for Psychiatry). The average age of the participants was 28.63 years (*SD* = 9.11). The research ethics committee of the canton Zurich approved the study protocol and informed consent was given prior to the inclusion to the study.

2.2. Procedure

An isometric dynamometer (Zühlke Engineering and Sensory-Motor Systems Laboratory ETH Zurich; measuring range: 0–600 N) was used to assess participant's MVC and allow them to exert effort. Before detailed instructions to the task were given, participants were asked to grip the hand dynamometer with their dominant hand as hard as possible in two consecutive trials of 3.5 s. No visual feedback of applied grip force was given in these calibration trials. MVC was calculated taking the median force value of the period 1–3.5 s of these two maximum effort trials.

Participants were then presented with a series of choices between a *no effort/low reward* and a *high effort/high reward* option on a 19-in. computer screen and indicated their choice by button-press (see Fig. 1). The *no effort/low reward* option yielded a reward of 1 Swiss Franc (CHF; 1 CHF ≈1.07$), while the effortful option required 10/50/90/100% MVC and was rewarded with 1/1.5/2/2.5/3/5 CHF. The corresponding effort cost was implemented after each choice in a 3.5 s effort period with visual feedback. This effort period was also implemented if the *no effort/low reward option* was chosen. Thus, time costs were held constant in all options.

The criterion for success was the median force values achieved minus 5%. A relative margin was used to keep the risk of achieving the criterion independent of effort exerted. Moreover, to prevent exclusive choice of the *no effort/low reward* option due to risk aversion, participants were given the default reward of 1 CHF when failing to hold the required effort level in the *high effort/high reward* option. These measures were successful: the number of trials in which participants failed to reach criterion was low (1.21 trials out of 72 trials, 1.7%; *SD* = 1.82 trials) and not related to choice parameters ($p > 0.58$). Considering this, failed trials remained in the analysis as choices to exert effort. Incidentally, the small number of failed trials also indicates that participants behaved as instructed in the task. Participants could have always or in 50% of the trials chosen the effortful option even if they did not intend to actually exert effort because the monetary outcome would have been the same as that of the no effort option. However, such behavior would result in considerably higher failure rates, which were not observed in the present study.

Each decision pair was presented three times, resulting in a total of 72 trials, which were divided in three randomized blocks. Time for choice was not restricted. Response times were determined as the period from presentation of the two options to selection of one of them in milliseconds (ms). Participants were instructed to rest only during breaks between blocks. To control for effects of fatigue, we assessed an additional MVC measure (identical to the one described above) immediately after finishing the experiment. Participants were further instructed that, after completion of the task, five of the 72 trials would be randomly drawn and paid out.

2.3. Data analysis

To investigate group level effects of effort and reward on choice and response times, we applied repeated measures ANOVA with fraction of effortful choice and response times as the dependent variables and the factors effort and reward as independent variables. For each participant we then estimated indifference points in the different effort conditions (10/50/90/100% MVC). These indifference points were estimated by fitting a logistic function to the proportion of effortful choices, plotted as a function of the reward in the effortful option (1/1.5/2/2.5/3/5 CHF). The indifference point is therefore the amount at which the probability of choosing to exert effort was 0.5. In other words, we used choices to determine by a logistic fit the monetary amount for which participants would be indifferent between (i.e., choose equally often) the no effort and the high effort option (see Fig. 2).

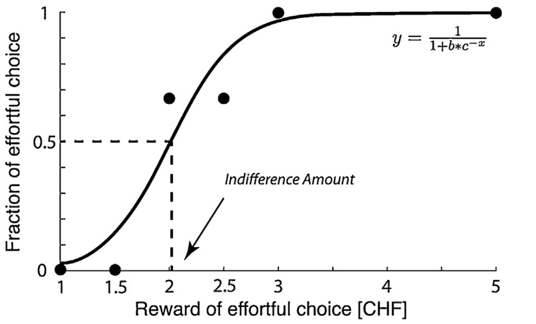


Fig. 2. Choice data (fraction of effortful choice) of subject 4 plotted against all rewards in the 90% effort condition and the logistic function fit.

The subjective value (SV; "utility") of the effort requirements (10/50/90/100% MVC) was then obtained by dividing the standard 1 CHF (effortless option) by the respective indifference point for the effortful option. We then fitted three different models (Eqs. (1)–(3)) to group data using regression techniques (EzyFit Matlab Toolbox) yielding appropriate parameter estimates and R^2 values. For individual level model comparison the a-parameters were replaced with the fitted group level parameter. Note that these functions can only be interpreted as pure effort discount functions under the assumption that for monetary reward SV increases linearly with its objective value.

Eq. (1) is a simple linear model.

$$SV = a - k * Effort \quad (1)$$

Eq. (2) constitutes Mazur's hyperbola (Mazur, 1987).

$$SV = \frac{a}{1 + k * Effort} \quad (2)$$

Finally we modeled choice data with a quadratic function (Eq. (3)).

$$SV = a - k * Effort^2 \quad (3)$$

In order to keep the number of free parameters the same for the three different models we assumed an exponent of 2 in the parabolic model, which has been reported by Stevens and Mack (1959) for ratio and magnitude production procedures on a hand dynamometer. To determine whether the assumption was justified we fitted the exponent separately in our data and obtained a value of 2.24 for the overall function and a mean of 2.48 (SD = 1.29) for individual functions. Thus, the fitted values were close to 2. Moreover, the individual values were not significantly different from 2 although there was a trend toward an increase ($t(23) = 1.83$, $p = 0.081$).

3. Results

The mean MVC of participants was 233.11 N (SD = 86.30 N). Male and female participants did not significantly differ in their grip strength (M = 261.84 N, SD = 94.53 N, M = 218.74 N, SD = 81.18 N, $t(22) = 1.16$, $p = 0.26$). Pre- and post experiment measures of MVC (M_{pre} = 233.11 N, SD_{pre} = 86.30 N, M_{post} = 222.14 N, SD_{post} = 72.28 N) were not significantly different ($t(23) = 1.20$, $p = 0.24$), suggesting that participants did not show significant muscle fatigue. Average earnings in the task were 10.31 CHF (SD = 2.15).

Between-subject differences in a fatigue index (MVC_{pre}/MVC_{post}) did not significantly predict choice in the different effort conditions (all $p > 0.28$). Moreover, "stronger" participants (high MVC_{pre} as determined by a median split) did not differ from "weaker" participants in terms of effort discounting (area under the curve measure of subjective value, $t(22) = 0.44$, $p = 0.67$).

A two-way repeated measures ANOVA for the fraction of effortful choice (Fig. 3a) revealed highly significant main effects of effort ($F(1.88, 43.24) = 53.62$, $p < 0.001$, $\eta^2_p = 0.700$) and reward ($F(2.48, 57.04) = 166.90$, $p < 0.001$, $\eta^2_p = 0.879$) and also a significant interaction term ($F(4.75, 109.14) = 11.79$, $p < 0.001$, $\eta^2_p = 0.339$). In addition, for response time data (Fig. 3b) we also found significant effects for effort ($F(3, 69) = 17.57$, $p < 0.001$, $\eta^2_p = 0.433$), reward ($F(5, 115) = 7.71$, $p < 0.001$, $\eta^2_p = 0.251$), and the interaction term ($F(15, 345) = 3.23$, $p < 0.005$, $\eta^2_p = 0.123$). These data suggest that participants processed both effort and reward information.

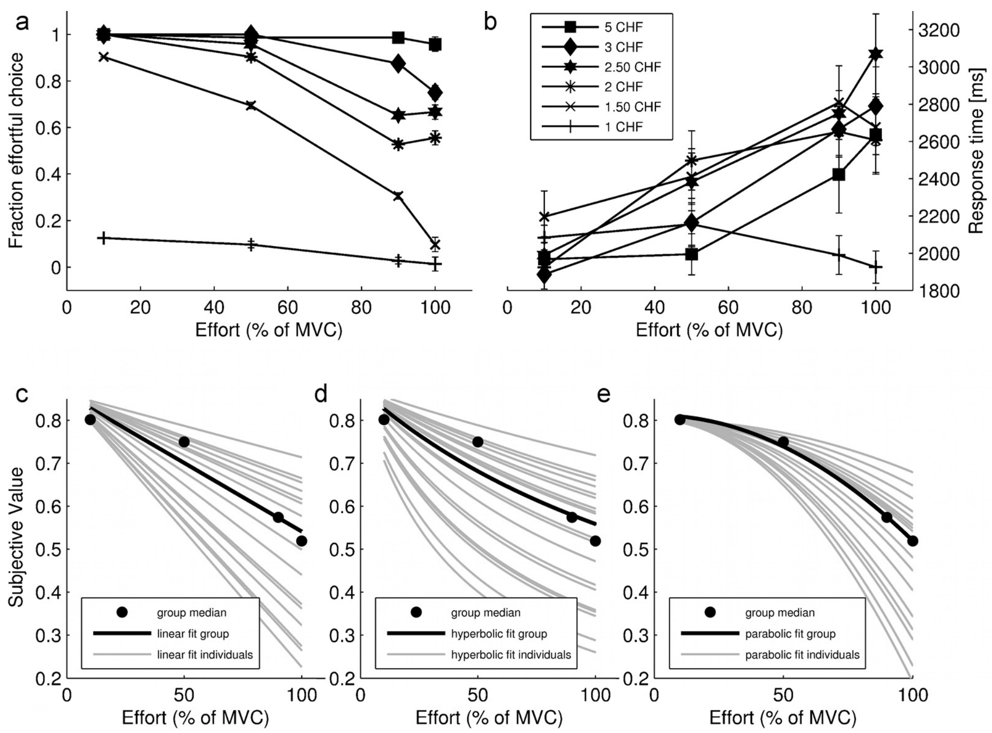
Next, we assessed the three different models in how well they explained choice. On the group level the parabolic model explained 99.68% of the variance of median subjective values (Fig. 3c) and was superior to linear and hyperbolic models (R^2 linear: 0.9348, R^2 hyperbolic: 0.8673, see Fig. 3c–e). A similar pattern emerged also with the respect to model fits on the individual level (R^2 linear: 0.8299, R^2 hyperbolic: 0.7680, R^2 parabolic: 0.9087). The parabolic function performed best in 18 out of the 24 subjects (linear: 5, hyperbolic: 1). The difference between the best and second-best models (parabolic and linear, respectively) was significant according to a Wilcoxon signed-rank test ($p < 0.01$). Moreover, residuals in the linear and hyperbolic model show characteristic under- and overestimations, while this is not the case in the parabolic model. Thus, the parabolic model explains effort discounting better than the other models we considered.

4. Discussion

The primary aim of the present study was to investigate the functional form of the discounting of monetary rewards by physical effort. We fit three different models to our data: a linear, a hyperbolic and a parabolic model. The parabolic model clearly outperformed the other models on both the group and the individual level. Stevens (1957) postulated that objective force properties in physical effort would translate into subjective experience according to a power function. Our results suggest that this principle can be expanded to value-based decision-making involving effortful choice options.

In everyday language, *effort* is a multifaceted concept. Normally, it does not only involve physical, but also mental effort and time costs (among others). If experiments are performed using this conglomerate *effort* term it is impossible to tease apart the different costs and make inferences about effort discounting. In the present experiment physical effort was operationalized in terms of muscular force scaled up to the subjective maximum, while mental effort demands and time costs were held constant. In this framework, it is intuitive and has previously been shown in psychophysical experiments (e.g., Stevens and Mack, 1959) that, as muscle force approaches subjective maximum, the sense of effort increases according to a power function. Consequently the discount function would take a concave form, which is consistent with our results.

Previous studies have usually considered one discounting function, particularly linear or convex (hyperbolic) ones and generally reported good fits of the data (Mitchell, 1999, 2003, 2004; Prévost et al., 2010; Sugiwaka and Okouchi, 2004). However, it is conceivable that alternative functions would have provided even better fits. Moreover, it is important to note that the present study ensured that the time of effort exertion and the probability of achieving different effort levels were constant (see Section 2). This is important because time and decreasing probability is discounted in a hyperbolic fashion. Less stringent control of probability or time could therefore explain why some studies of effort discounting found a good fit with hyperbolic models. This notion is consistent



n fraction of effortful choice (a) and response times (b) for different monetary rewards and effort levels (error bars represent standard errors of the mean).
: partly covered by data labels. (c–e) Group and individual fits of SV for the linear, hyperbolic, and parabolic model (Eqs. (1)–(3)).

l evidence for hyperbolic effort discounting reported t work of Mitchell (1999, 2003, 2004).

t study constitutes a pilot and holds one primary he 10 and 50% effort conditions, a large part of the ınd 46%) only showed effort avoiding choice when red the same amount for the effortless and effortful . At the next higher reward level (1.5 CHF), they all tful option. Thus, the determination of the indiffer- ; relatively imprecise and the best approximation of nce points giving our data lies in the middle between logistic fit). As a consequence, our procedures under- for these effort levels (and hence overestimated low effort levels). Therefore, the intercept of the dis- had to be fitted on the group level rather than fixing ıntly though, this underestimation of SV would not avity of the function. In future studies, a more fine- should be applied, also sampling very low reward he intercept can be fixed at 1. Future research may ncorporate a separate measure of subject-specific at the different effort-levels. This would possibly apart the purely psychophysical and the decision- of effort discounting, although this would not affect s of the present findings.

r clinical applications of our effort-discounting task, th respect to aberrant motivational states in depres- enia as well as neurological disorders. For example, uction in motivation and goal-directed behavior – observed in these disorders and is strongly linked ınctioning (Foussias and Remington, 2010; Marin, ical observation apathetic patients are less willing t to obtain a reward, which could be reflected in a t discount function. Whether this affects the shape or only the discount factor is an interesting empir- One hypothesis would be that apathetic patients rds stronger than healthy subjects even when only moderate amounts of effort are required. In this case the discount function could either approach a linear pattern or remain parabolic but become steeper. Compared to other effort tasks that have been applied in clinical populations (Gold et al., 2013; Treadway et al., 2012), the present task removes the confounding effect of time, allows easy understanding of the choice situations and demands minimal cognitive capacity for predicting effort costs because the expenditure is immanent.

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Appendix B: Paper 2

"Apathy But Not Diminished Expression in Schizophrenia Is Associated With Discounting of Monetary Rewards by Physical Effort".

This is a pre-copy-editing, author-produced PDF of an article accepted for publication in *Schizophrenia Bulletin* following peer review. The definitive publisher-authenticated version (Hartmann, M. N., Hager, O. M., Reimann, A. V., Chumbley, J. R., Kirschner, M., Seifritz, E., Tobler, P. N., Kaiser, S., in press. Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort. *Schizophrenia Bulletin*) is available online at:

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Apathy but not Diminished Expression in Schizophrenia is Associated With Discounting of Monetary Rewards by Physical Effort

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Keywords:	negative symptoms, effort-based decision-making, cost-benefit calculation

Apathy but not Diminished Expression in Schizophrenia is Associated With Discounting of Monetary Rewards by Physical Effort

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Abstract

Negative symptoms in schizophrenia have been grouped into the two factors of *apathy* and *diminished expression*, which might be caused by separable pathophysiological mechanisms. Recently, it has been proposed that apathy could be due to dysfunctional integration of reward and effort during decision-making. We asked whether apathy in particular is associated with stronger devaluation ("discounting") of monetary rewards that require physical effort.

Thirty-one patients with schizophrenia and 20 healthy control participants performed a computerized effort discounting task in which they could choose to exert physical effort on a handgrip to obtain monetary rewards. This procedure yields an individual measure for the strength of effort discounting.

The degree of effort discounting was very strongly correlated with apathy, but not with diminished expression. Importantly, the association between apathy and effort discounting was not driven by cognitive ability, antipsychotic medication or other clinical and demographic variables.

This study provides the first evidence for a highly specific association of apathy with effort-based decision-making in patients with schizophrenia. Within a translational framework the present effort discounting task could provide a bridge between apathy as a psychopathological phenomenon and established behavioral tasks to address similar states in animals.

Key words: negative symptoms/effort-based decision-making /cost-benefit calculation

Introduction

Negative symptoms are a core feature of schizophrenia and have a strong impact on functional outcome.[1-4] Although the detrimental functional consequences of negative symptoms are well recognized, causal mechanisms still remain largely unknown, hindering the development of effective treatment. Recently, a consensus has emerged that negative symptoms can be grouped into two factors,[5-7] which we refer to as *apathy* and *diminished expression*. It has been proposed that these two dimensions could be caused by partly different pathophysiological mechanisms.[6, 8] Apathy can be defined as a reduction of motivation and/or goal-directed behavior.[9] Reward is considered a driving factor for both motivation and goal-directed behavior. Accordingly, deficits in reward learning,[10, 11] the neural representation of reward anticipation,[12] and the ability to form mental representations of prospective rewards[13] have been put forward as correlates of apathy. More recently, research into negative symptoms has proposed that goal-directed behavior is not solely driven by the reward component itself, but also the effort required to obtain the reward.[14-16] Consequently, an overweighing of effort costs in decision-making could result in a decrease of goal-directed behavior and present clinically as apathy. Two important studies report dysfunctions of effort-based decision-making in patients with schizophrenia, but the expected symptom-level link between apathy and choice behavior was not observed in patients[14, 15].

Here, we employed an approach informed by behavioral economics to specifically address the relationship between negative symptoms and making decisions involving widely different levels of real and pure physical effort.[17, 18] Specifically, we adapted a standard choice paradigm[19] to provide a subjective measure of how monetary reward is devalued in proportion to a requirement for handgrip force (*effort discounting*).[20] In other words, we measured one's propensity to refrain from engaging in a rewarded but effortful behavior. We hypothesized that steeper effort discounting could account for the reduction of motivation and goal-directed behavior in apathetic patients relative to a healthy control group and to patients with lower apathy levels. In particular, we hypothesized that increased effort discounting would be correlated with apathy but not with diminished expression ratings.

Methods

Participants

Thirty-one individuals meeting DSM-IV[21] criteria for schizophrenia (n = 25) or schizoaffective disorder (n = 6, no mood episode) and 20 healthy control (HC) participants took part in the study. The local Ethics committee approved the study and all participants gave written informed consent. Patients were clinically and pharmacologically stable inpatients at the end of their hospitalization (n = 25) or outpatients (n = 6) treated at the Psychiatric Hospital, University of Zurich. Please note that the average inpatient stay for patients with schizophrenia in Swiss psychiatric hospitals is above 40 days,[22] thus many of our inpatients would be treated as outpatients in other health care systems. Importantly, inpatients participated in a multimodal treatment program and were encouraged to engage in activities outside the hospital, which allowed assessment of negative symptoms. Patients were excluded if (1) daily *lorazepam* dosage exceeded 1 mg, (2) florid positive symptoms were present (Positive and Negative Syndrome Scale; PANSS;[23] any positive subscale item score > 4), (3) extrapyramidal side-effects were observed by the treating clinician or (4) additional DSM-IV axis-1 or axis-2 diagnostic criteria were met (according to the treating clinician). To confirm axis-1 diagnosis in patients, exclude comorbid axis-1 disorders and ensure the absence of axis-1 disorders in the HC group we employed the Mini-International Neuropsychiatric Interview (M.I.N.I.).[24]

Assessment of Psychopathology and Cognition

For psychopathological assessment the following instruments were used: Brief Negative Symptom Scale (BNSS),[25] Scale for the Assessment of Negative Symptoms (SANS),[26] PANSS, Global Assessment of Functioning (GAF) scale,[27] Personal and Social Performance Scale (PSP),[28] and the Calgary Depression Scale for Schizophrenia (CDSS).[29] The BNSS was translated into German by the senior author (see supplementary material), who trained and regularly supervised all raters. The scores for the two negative symptom factors in the BNSS were calculated according to the two-factor structure proposed by the original authors (see supplementary table S1).[30]

A composite cognitive ability score was computed as the mean of z-transformed scores (based on HC group data) of the following cognitive tests: verbal learning (German version of the Auditory Verbal Learning Memory Test; VLMT),[31] verbal and visual short-term and working memory

(Digit Span,[32] Corsi block-tapping test)[33], processing speed (Digit-Symbol Coding),[34] planning (Tower of London),[35] and semantic and phonemic fluency (animal naming, s-words).[36]

Experimental Procedure: Effort Discounting Task

The procedure constitutes an adapted version of a recently described effort discounting task[20] (figure 1). An isometric dynamometer (Sensory-Motor Systems Laboratory ETH Zurich; measuring range: 0 – 600 Newton) was used to assess physical effort. To determine maximum voluntary contraction (MVC) participants were asked to squeeze the handgrip with their dominant hand as hard as possible for two consecutive trials of 3.5 s without visual feedback of their grip strength. To approximate realistic steady-state values, MVC corresponded to the median force value of the period 1 - 3.5 s of these two maximum effort trials.

During the task participants then made a series of choices between a default small amount of money available without any effort and an alternative larger amount that was conditional on physical effort exertion. Participants indicated their preference by button-press. The effortful option was manipulated over successive trials in terms of reward (1.5, 2, 2.5, 3, 5 Swiss Francs; CHF; 1 CHF ≈ 1.09 $) and effort (40, 60, 80, 100 % MVC), while the default effortless option always yielded 1 CHF. Each option pair was randomly presented four times, resulting in a total of 80 trials, which were divided in two blocks. Time for choice was not restricted. Please note that for a minority of participants and effort levels reward had to be iteratively decreased or increased in additional trials for more accurate estimation of effort discounting indices (see *Data Processing*).

The effort level of the chosen option had to be implemented after each choice in constant 3.5 s effort exertion periods with visual feedback (critical measurement period: 1 - 3.5 s). Importantly, the duration of the effort period was also implemented if the default effortless option was chosen. Thus, time costs were held constant between the effortful and effortless options. The individually adjusted effort levels assured that the participants were physically capable of performing each effort level. To exclude effects of loss aversion, participants were given the default reward of 1 CHF when failing to hold the required effort level (the number of failed trials was low and thus remained in the analyses as choice data; M = 1.2, SD = 1.68). To control for effects of fatigue, we collected an additional MVC measure (identical to the one described above) after finishing the experiment. Five of the total completed trials were randomly drawn and paid out after completion of the task. Please note that no feedback about earnings was given during the task. The task was implemented using the MATLAB toolboxes *Cogent 2000* and *Cogent Graphics* and presented on a 19-inch computer screen.

Visual Analog Scales: Monetary Reward Pleasure and Perceived Effort

After the effort discounting task, participants provided self-report measures of anticipated monetary reward pleasure (how much pleasure they would feel when unexpectedly finding a 50 CHF bill on the street) and effort perception (how strenuous they perceived 40, 60, 80, and 100 % MVC) on visual analog scales (VAS).

Data Processing

Intuitively, the effort discounting task aims to identify the minimum amount of payment each subject demands before agreeing to exert a given effort. More precisely, this is the amount of payment that makes them indifferent between the effortless and a given effortful option. To extract the indifference points, a logistic function was fitted to the fraction of effortful choices across all reward levels (figure 2A). Overall model fit (R^2) was not different between the patient and HC group ($t(49) = 1.16$, $p = 0.25$). These indifference values (figure 2B) then served to capture how the different effort levels (40, 60, 80, and 100% MVC) reduce (i.e., "discount") value in each participant. To do so, the default reward (1 CHF) was divided by the respective indifference amount, which yields a measure of relative subjective value (SV; figure 2C). Indifference points were estimated online during the task and if no preference reversal was observed, the reward amount for the effortful option was iteratively increased (7/10/20 CHF) or decreased (1.20/1.10/1.05 CHF) in additional three steps until choice behavior reversed.

In discounting paradigms the indicator for the degree of discounting has traditionally been the fitted parameter of a model with one free parameter that modulates the steepness of the curve.[37] However, debate has recently arisen about the appropriate shape of that curve in effort discounting.[20] In order to circumvent this issue and capture individual effort discounting in an unbiased way, we computed the area under the curve (AUC) of the relative SVs over the four effort conditions as the measure for overall discounting (figure 2C). A smaller AUC corresponds to steeper effort discounting. This procedure is entirely driven by the data but has comparable sensitivity to a one-parameter discount model.[38] In sum, for each participant we have thus a measure of overall discounting (AUC) and measures for the four effort levels separately (relative SVs).

Statistical Analyses

To test our main hypothesis, we computed Pearson correlations (r) between negative symptoms (apathy and diminished expression) and overall effort discounting (AUC). To further test for a significant difference between these correlations we computed a t-statistic.[39] Additionally, we calculated Bayes factors (BF_{10}) on these correlations,[40] allowing us to quantify evidence in favor of the null hypotheses in the case of non-significant correlations. To control for confounds partial correlations were computed.

We then pursued a categorical approach to compare effort discounting of the HC group to LOW-APATHY and HIGH-APATHY patients using the median split on the BNSS apathy score (Mdn = 16). We conducted a 4 (relative SVs for the four effort levels) × 3 (HC, LOW-APATHY, HIGH-APATHY) mixed design ANOVA to investigate overall group effects and additional ANOVAs to detect specific effects.

Please note that if variables were non-normally distributed according to Shapiro-Wilk tests, non-parametric statistics (Spearman correlation r_s, Mann-Whitney U-test) were applied.

Results

Sample Characteristics

Group characteristics and group comparisons are depicted in table 1.

Effort Task Performance

All participants demonstrated preference reversal for all effort levels and showed overall effort discounting (decreasing relative SVs with increasing effort), which indicates that they processed both effort and reward information. For raw choice data please see supplementary figure S1. The HC and the patient group did not differ significantly with regard to MVC before the experiment, time to reach MVC, fatigue, and final payout (table 1). None of the groups showed significant fatigue (decline in MVC before vs. after the experiment; ps > 0.23). There was no significant correlation of apathy with MVC before the experiment ($r(29) = 0.12$, $p = 0.51$), fatigue ($r(29)$ = -

0.18, p = 0.34), final payout ($r(29)$ = -0.30, p = 0.10), and total number of trials completed ($r_s(29)$ = -0.17, p = 0.36).

Association of Negative Symptoms with Effort Discounting

We used AUC of the relative SVs to determine overall effort discounting. Regarding our main hypothesis we found a highly significant correlation between apathy and effort discounting ($r(29)$ = -0.67, p < 0.0001; figure 3A). In contrast, the correlation between diminished expression and effort discounting was not significant ($r(29)$ = -0.14, p = 0.45; figure 3B). Importantly, these two correlations between symptomatology (apathy vs. diminished expression) and effort discounting were significantly different ($t(28)$ = 4.57, p < 0.0001). Strikingly, the differential correlations arose even though, in line with prior studies on the structure of negative symptoms.[5, 7, 41, 42], apathy and diminished expression were significantly correlated with each other ($r(29)$ = 0.58, p < 0.01). Thus, our results indicate that effort discounting is more strongly associated with apathy than diminished expression.

To quantify the relative evidence for the null (H_0) or the alternative hypothesis (H_1) in these correlations we performed "Bayesian hypothesis tests".[40] These analyses revealed a BF_{10} of 624.81 in the correlation between apathy and effort discounting, and a BF_{10} of 0.18 in the correlation between diminished expression and effort discounting. By accepted convention,[43] the first implies "decisive evidence" for the H_1 (BF_{10} > 100), while the latter implies "substantial evidence" for the H_0 (BF_{10}: 0.1 - 0.33). In other words, there is decisive evidence for the association between apathy and effort discounting and substantial evidence for the lack of an association between diminished expression and effort discounting.

We next computed a non-parametric partial correlation between apathy and effort discounting, controlling for depressive symptoms, MVC, fatigue, chlorpromazine equivalents, cognitive ability, age, education, and income. Importantly, the association between clinically assessed apathy and our measure of effort discounting remains highly significant even when we control for variance in all the considered factors ($r_s(21)$ = -0.59, p < 0.01) indicating that these factors cannot account for the observed association.

Association of Covariates with Effort Discounting

We also conducted further correlational analyses between the covariates in our study and effort discounting (table 2; see supplementary table S2 for correlations with SVs at each effort level). Three main results from these analyses have to be highlighted: first, the main finding of the study – apathy but not diminished expression is associated with effort discounting – also holds when the SANS is used to quantify symptoms. Second, no significant correlations with positive symptoms, depression and chlorpromazine equivalents[44] were obtained. Finally, in both, patient and HC groups, cognition, education, income, and MVC were not significantly associated with effort discounting.

Self-report Measures of Monetary Reward Valuation and Perceived Effort

There were no significant effects of group (HC, LOW-APATHY, HIGH-APATHY) on self-report measures of either monetary reward valuation or perceived effort (see supplementary figures S2A and S2B). To investigate possible antecedents of increased effort discounting in apathetic patients we correlated effort discounting and apathy with the perceived effort in the four effort levels (AUC) and the self-report measure of anticipated monetary reward pleasure. First, none of the measures for perceived effort were associated with apathy in the patient group (all ps > 0.46, all $BF_{10} < 0.18$). This indicates that altered effort-based decision-making in apathetic states does not seem to be primarily driven by changes in the pure psychophysical translation of physical force to sensation. Second, anticipated pleasure derived from monetary reward was negatively correlated with apathy ($r(29) = -0.43$, $p = 0.02$). Furthermore, effort discounting was associated with less anticipated pleasure, but not with perceived effort (see table 2). These data suggest that the relationship between apathy and effort discounting in patients might be partly driven by a reduction in anticipated pleasure. However, when controlling for reward pleasure in a partial correlation between apathy and effort discounting the resulting coefficient remains highly significant ($r(28) = -0.59$, $p = 0.001$), suggesting that reward pleasure fails to completely account for the relation between apathy and effort discounting.

Group Differences in Effort Discounting

To assess how effort discounting in high and low apathy patients compares to, and differs from, effort discounting in HC we median-split the patient group. Group level results are depicted in figure 3C. In the 4 (relative SVs for the four effort levels) × 3 (HC, LOW-APATHY, HIGH-APATHY) mixed design ANOVA we observed a significant main effect of group ($F(2,48) = 5.81$, $p < 0.01$) and effort ($F(3,48) = 119.33$, $p < 0.0001$), and a nearly significant interaction term ($F(6,48) = 2.12$, $p = 0.054$). Follow-up 4 × 2 mixed design ANOVAs showed that the HC and the LOW-APATHY group did not significantly differ ($F(1,33) = 0.04$, $p = 0.84$), while the HIGH-APATHY group was significantly different from both the LOW-APATHY and HC group ($F(1,29) = 8.40$, $p < 0.01$; $F(1,34) = 10.90$, $p < 0.01$).

We further computed one-way ANOVAs for all the effort levels (factor group: HC, LOW-APATHY, HIGH-APATHY) and found significant group effects in the 40%, 60%, and 80% effort levels ($F(1,33) = 5.22$, $p < 0.01$; $F(1,33) = 4.15$, $p < 0.05$; $F(1,33) = 5.45$, $p < 0.01$). Post hoc comparisons using the Fisher LSD test further revealed significant differences ($p < 0.05$) indicative of stronger effort discounting with more apathy in the 60% and 80% condition (HIGH-APATHY group versus both the HC and LOW-APATHY group). Moreover, in the 40% condition both patient groups discounted significantly more than the HC group. In sum, the HIGH-APATHY group shows stronger effort discounting than the LOW-APATHY and HC group across a broad effort range, while the only effort level where both patient groups can be statistically distinguished from the HC group is the low 40% effort level.

To investigate whether effort discounting was stable over the course of the experiment we split choice data into four blocks and computed a mixed-design ANOVA on fraction of effortful choice. This analysis revealed no significant main effect of group ($F(2,48) = 2.08$, $p = 0.14$), a trend-level main effect of block ($F(3,48) = 2.55$, $p = 0.07$), and a trend-level block x group interaction ($F(6,48) = 2.02$, $p = 0.07$).

Discussion

In the present study, we adapted a paradigm from behavioral economics to investigate how the discounting of monetary rewards by physical effort requirements is associated with the two factors of negative symptoms in schizophrenia - apathy and diminished expression. We have several key findings to report. First and most importantly, increased effort discounting was very strongly correlated with apathy but not with diminished expression. This effect was not due to depressive symptoms, grip strength, fatigue, antipsychotic medication dosage, cognitive impairment, age, education, and income. Second, our data suggest that increased effort discounting in apathy is due to deficits in both weighing of effort cost in decision-making and the anticipated value of reward. Third, group comparisons revealed that only HIGH-APATHY patients showed overall differences in effort discounting compared to the HC participants.

To our knowledge, this is the first study to show that a decreased willingness to exert physical effort for a secondary reward is negatively correlated with apathy but not with diminished expression within a schizophrenia sample. Two important recent studies also reported a decreased willingness to exert effort for monetary rewards in schizophrenia.[14, 15] Our results are generally in line with those two studies, but some differences have to be pointed out. In both studies the effect mainly surfaced in group comparisons, either between a patient and a HC group,[15] or two patient groups (high and low negative symptoms) and a healthy control group.[14] It is of note that Fervaha and colleagues[15] computed across-group correlations (pooling HC and patient groups) and found significant results in the association between apathy and effort-based decision-making using this approach. However, they reported no significant correlations within the patient group. Interestingly, Gold and colleagues[14] also applied the BNSS, but they found a significant effect only when the group median split was performed with the total negative symptom score. No group differences were apparent when the split was based on the apathy factor. The authors considered this as surprising, because their theoretical framework predicted that apathy in particular would be associated with effort-based decision-making. There are several differences in the experimental task between these studies and our present study that might explain the partial discrepancies in the results. First, instead of operationalizing effort as number of button presses on a computer device, we used different levels of physical force exerted on a handgrip that was calibrated according to the participant's maximum grip strength. This procedure has the advantage that we keep time costs constant and are thus able to interpret our results as pure effort discounting independent of delay discounting. Moreover, handgrip effort exertion is less likely to be susceptible to an influence of motor symptoms, because to our knowledge deficits in pure force application have not been observed in patients with schizophrenia.[45] In line with this notion, we found no difference in MVC and time to reach MVC between patients and healthy controls. Second, we aimed for a task structure with easily understandable choice options and consequently restricted our cost manipulation to physical effort. In the previous studies both effort and probability costs were manipulated, which might lead to a different pattern of associations with psychopathology. This difference between studies could also account for the lack of association between effort discounting and cognitive ability in our study. Third, our present task incorporates a wide range of effort levels from small to maximum, which is likely to increase overall sensitivity.

In our group analyses the combined patient group differed significantly from HCs only in the 40% effort condition (figure 3C). HCs discount less in lower effort levels, which is consistent with data from a previous study of our group.[20] Since this pattern is absent in the patient group, it can be hypothesized that groups not only show differences in overall discounting, but also in the distinct form of discounting. It is also noteworthy that group differences at the highest effort level are not significant. In other words, choice variance and intergroup differences seem to decrease with increasing effort.

A decision whether to pursue a potentially rewarding behavior when effort is involved is mainly determined by subjectively weighing reward against effort costs. Here we show that, based on choice data, apathy is associated with stronger effort discounting. Post-test self-report assessments of monetary reward and the performed effort levels provide us with additional information about how these two decision components are perceived. Please note that these measures do not reflect in-the-moment experience of effort and reward. The perceived effort for the four subjectively calibrated levels seems to be comparable across groups and not associated with symptoms or effort discounting. Self-reported anticipated reward pleasure as a measure of reward representation was associated with both apathy and effort discounting. This is in line with the notion that negative symptoms are linked to aberrant mental representation of anticipated reward,[13] but stands in contrast to results reported in the discussed study by Fervaha and colleagues,[15] who used a similar measure but did not report any associations with symptoms. The significant partial correlation between apathy and effort discounting, controlling for perceived reward, indicates that the strong relationship between apathy and effort discounting can only partially be accounted for by degraded reward representations.

Some limitations should be noted in relation to the present study. Most of our patients were inpatients with moderate levels of negative symptoms. Although all inpatients were well stabilized and had the opportunity to engage in a variety of activities, it would be important to assess generalizability in an outpatient sample. Moreover, sample size was modest (n = 31). Although our main effects are very strong, one has to consider this in particular regarding the missing association between perceived effort and effort discounting or apathy. It has to be further mentioned that our effort perception measure was assessed post-test, which constitutes a retrospective estimation of in-the-moment experience that might be influenced by effort expenditure during the task. Future studies should assess cigarette smoking characteristics of participants since this might affect effort discounting.[46] Finally, our study design only included money, which is a secondary reward. Thus, we are not able to generalize our results to the discounting of primary rewards (e.g., food, sex) by effort, which have been shown to be partially processed by different brain regions.[47] Future studies should also investigate how cognitive effort costs are processed in relation to apathetic states. It has been suggested that cognitive and physical effort might be driven by common neural systems.[48] We would thus hypothesize that apathy is also associated with stronger cognitive effort discounting.

The strong link between effort discounting and the negative symptom dimension apathy contributes to a translational approach to the symptoms of schizophrenia.[49, 50] Within this framework a human behavioral task as employed in the present study provides an essential bridge between human psychopathology and behavioral tasks to assess related phenomena in animals. For this bridging role our task seems to be very well suited for two main reasons: First, effort discounting in our binary choice task shows a very strong and specific relationship with the apathy dimension, which is not affected by the major possible confounds. Second, although our task is not equivalent to rodent tasks, it provides a close approximation. Importantly, similar to T-maze tasks in rodents,[51] we employ a simple binary choice independent of probability costs. A translational framework including human and animal tasks for a specific psychopathological dimension can be employed to investigate pathophysiological mechanisms and pharmacologic compounds for specific symptoms. There are already promising causal models for negative symptoms – for example D2 receptor overexpression[52] – that could be investigated with available animal analogues of our effort-based choice task. Importantly, human and animal effort-based decision-making tasks could contribute to a model for preclinical testing of drugs aiming to reduce negative symptoms. Currently, most preclinical tests used in drug development for schizophrenia are unrelated to negative symptoms, such as prepulse inhibition[53] or amphetamine-induced hyperlocomotion[54]. In line with other authors we believe that new compounds[51, 55] should be developed in preclinical and clinical studies with tasks that have shown a strong relationship with the target negative symptom[50] - as exemplified by the relationship between effort-based decision-making and apathy.

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Table 1. Demographics, clinical variables, composite cognition score, and effort task performance.

	Patient Group (n = 31)	HC Group (n = 20)	Test Statistic ($t/\chi^2/U$)	p	LOW-APATHY (n = 15)	HIGH-APATHY (n = 16)	Test Statistic ($t/\chi^2/U$)	p
Age in years	30.42 (8.69)	32.10 (6.79)	U = 362.00	0.32	30.33 (6.32)	30.50 (10.67)	t = 0.05	0.96
Gender (male/female)	25/6	15/5	χ^2 = 0.23	0.63	11/4	14/2	χ^2 = 0.99	0.32
Handedness (r/l)	29/2	16/4	χ^2 = 4.24	0.14	14/1	15/1	χ^2 = 0.002	0.96
Formal education in years[a]	9.79 (1.66)	12.27 (3.88)	U = 428.00	**< 0.01**	9.93 (1.67)	9.66 (1.70)	U = 108.50	0.65
Number of hospitalizations	4.10 (2.74)	-	-	-	4.33 (3.13)	3.88 (2.39)	t = 0.45	0.64
Chlorpromazine equivalents (mg/day)	568.23 (409.97)	-	-	-	544.40 (352.60)	590.56 (487.98)	t = 0.31	0.76
Psychopathology								
BNSS *apathy*	16.55 (7.50)	-	-	-	10.73 (3.58)	22.00 (5.91)	U = 240.00	**< 0.001**
BNSS *diminished expression*	10.42 (6.97)	-	-	-	7.93 (5.23)	12.75 (7.72)	t = 2.02	0.05
SANS *apathy*[b]	12.68 (5.87)	-	-	-	8.73 (3.62)	16.38 (5.15)	t = 4.75	**< 0.001**
SANS *diminished expression*[b]	13.32 (9.46)	-	-	-	10 (6.96)	16.44 (10.59)	U = 162.00	0.10
PANSS *positive factor*[c]	11.29 (2.81)	-	-	-	6.53 (2.70)	7.88 (2.75)	U = 154.50	0.18
PANSS *negative factor*[c]	16.06 (6.01)	-	-	-	11.60 (3.48)	16.75 (5.79)	U = 189.00	**< 0.01**
GAF	50.65 (9.71)	-	-	-	56.33 (6.11)	45.31 (9.55)	t = 3.80	**0.001**
PSP (total)	53.51 (10.61)	-	-	-	60.60 (5.60)	46.88 (9.93)	t = 4.69	**< 0.001**
CDSS (total)	2.42 (2.41)	-	-	-	2.20 (2.16)	2.63 (2.15)	U = 139.50	0.45
Cognition[d]								
Composite cognitive ability	-0.87 (0.67)	0 (0.60)	t = 4.72	**< 0.001**	-0.73 (0.62)	-1.00 (0.70)	t = 1.16	0.26
Effort Task Performance								
MVC (N)	184.96 (58.88)	202.91 (65.26)	t = 1.02	0.31	177.55 (54.75)	191.91 (63.47)	t = 0.67	0.51
Time to reach MVC (s)	0.81 (0.17)	0.78 (0.16)	t = 0.75	0.46	0.79 (0.18)	0.83 (0.15)	t = 0.66	0.51
Fatigue (MVC1 – MVC2)	8.95 (40.34)	10.22 (50.25)	t = 0.10	0.92	21.08 (38.52)	-2.42 (39.99)	t = 1.66	0.11
Final payout (in CHF)	10.84 (3.70)	12.15 (3.05)	t = 1.32	0.19	11.70 (3.80)	10.03 (3.53)	t = 1.27	0.22
Total trial number	83.90 (3.52)	82.13 (3.02)	U = 404.00	0.05	82.40 (3.44)	81.88 (2.66)	U = 113.00	0.80

Note: Data are presented as means and standard deviations. Potential group differences were investigated using two-sample t-tests and chi-square for continuous and categorical data respectively. For non-normally distributed data Mann-Whitney U-tests were applied. All patients were receiving atypical antipsychotics at the time of testing. Three individuals were additionally medicated with low doses of typical antipsychotics. 7 were receiving an SSRI, 3 were receiving low doses of benzodiazepine, 1 was receiving a mood stabiliser, 2 were receiving zolpidem against insomnia.

Abbreviations: BNSS: Brief Negative Symptom Scale; SANS: Scale for the Assessment of Negative Symptoms; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; PSP: Personal and Social Performance Scale; CDSS: Calgary Depression Scale for Schizophrenia; MVC: Maximum Voluntary Contraction; N: Newton; s: Seconds; CHF: Swiss Francs.

[a]Compulsory education in Switzerland is 9 years.

[b]*Apathy* = Avolition/Apathy, Anhedonia/Asociality ; *diminished expression* = Affective Flattening or Blunting, Alogia

[c]*Positive factor* = P1, P3, P5, G9; *negative factor* = N1, N2, N3, N4, N6, G7

[d]Cognition data has been z-transformed based on the data of the HC group for each test separately. The composite cognitive ability score was computed as the mean of the z-transformed test scores on subject level.

Table 2. Bivariate correlations.

		Effort discounting (AUC)
Psychopathology		
BNSS apathy		**-0.67*** **
BNSS diminished expression		**-0.14**
SANS apathy[a]		**-0.56** **
SANS diminished expression[a]		**-0.17**
PANSS positive factor[b]		**-0.26**
PANSS negative factor[b]		**-0.25**
GAF		**0.51** **
PSP (total)		**0.58** **
CDSS (total)		**-0.11**[d]
Number of hospitalizations		**0.01**[d]
Chlorpromazine equivalents (mg/day)		**-0.12**
Cognition[c]		
Composite cognitive ability	SZ	**0.03**
	HC	***-0.04***
Income	SZ	**0.10**[d]
	HC	***-0.09***
Maximum Voluntary Contraction (MVC)	SZ	**-0.29**
	HC	***-0.35***
Anticipatory reward pleasure (VAS)	SZ	**0.41***
	HC	***-0.30***
Perceived effort (overall, VAS)	SZ	**-0.26**
	HC	***0.04***

Note: * $p < .05$, ** $p < .01$, *** $p < 0.001$
Abbreviations: BNSS: Brief Negative Symptom Scale; SANS: Scale for the Assessment of Negative Symptoms; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; PSP: Personal and Social Performance Scale; CDSS: Calgary Depression Scale for Schizophrenia; SZ: Schizophrenia patient group; VAS: Visual Analogue Scale.
[a]*Apathy* = Avolition/Apathy, Anhedonia/Asociality ; *diminished expression* = Affective Flattening or Blunting, Alogia
[b]*Positive factor* = P1, P3, P5, G9; *negative factor* = N1, N2, N3, N4, N6, G7
[c]Cognition data has been z-transformed based on the data of the HC group for each test separately. The composite cognitive ability score was computed as the mean of the z-transformed test scores on subject level.
[d]Spearman correlations (r_s).

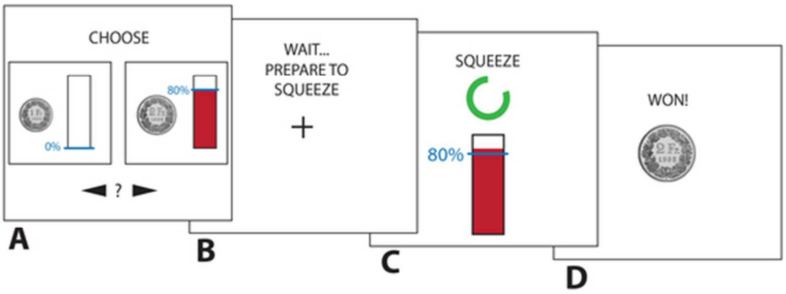


Fig. 1. Schematic of the effort discounting task. (A) Presentation of choice options (no time limit). (B) Fixation cross (4 s). (C) Effort exertion period (3.5 s). (D) Feedback period (3 s).
48x18mm (300 x 300 DPI)

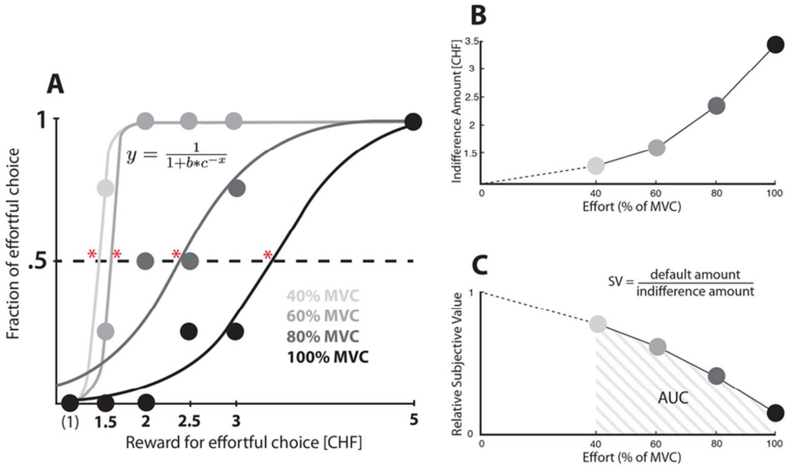


Fig. 2. Effort discounting. (A) Choice data from one participant and illustration of how we estimate the indifference points. In particular, we used a logistic function to interpolate the precise amount of reward that each participant required in order to be completely indifferent between the effortful and effortless options, i.e. in order for them to choose each option at 50% probability (*). (B) Indifference points plotted against all effort levels in the example participant shown in (A). (C) Discount curve of the same participant. The relative subjective values are calculated by dividing the default amount (1 CHF) by the indifference amount. The AUC of the relative subjective values constitutes our main dependent variable of overall individual effort discounting.
76x45mm (300 x 300 DPI)

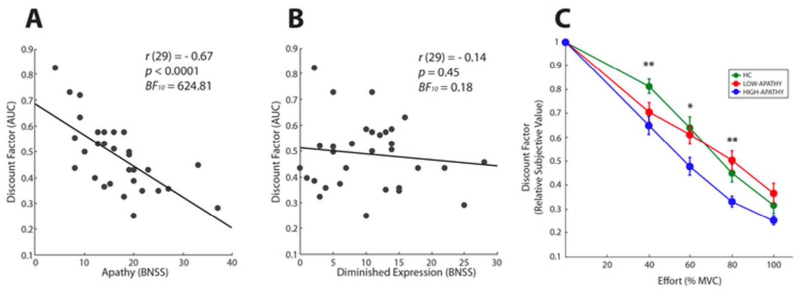


Fig. 3. Bivariate Pearson correlation (including significance test and Bayes factor) of apathy (A) and diminished expression (B) with the effort discount factor, measured as the AUC of the relative subjective values plotted against the four effort levels. (C) Group level effort discounting plotted against all effort levels (* = p < 0.05, ** = p < 0.01).
62x23mm (300 x 300 DPI)

Supplementary Material

German Translation of the Brief Negative Symptom Scale (BNSS)

The BNSS was translated to German by the senior author of the study. A BNSS-naïve English native speaker, who is an attending psychiatrist, performed the back-translation. At the time of the present study initial validation data from 35 patients were available.

The factor structure of the German version was similar to the English original (see below) with factor loadings for apathy and diminished expression ranging from 0.58 to 0.98. Only the distress item was somewhat more ambiguous than in the English original with a factor loading of 0.32 on diminished expression. Since the results of this factor analysis were obtained from a relatively small sample, we decided to employ the factor structure proposed by the authors of the original BNSS. In addition, omitting the distress item from the diminished expression factor did not change the results of the correlational analyses with effort discounting (Pearson $r(29) = -0.12$, $p = 0.52$; Spearman $r_s(29) = -0.01$, $p = 0.96$; $BF_{10} = 0.17$).

Inter-rater reliability of the German version was excellent with an intra-class correlation coefficient (ICC) of 0.97 for the BNSS total score and ICCs of 0.84 to 0.97 for the subscales. Convergent validity was confirmed by a strong correlation of the BNSS total score with the Scale for the Assessment of Negative Symptoms (SANS) total score ($r(33) = 0.86$). Discriminant validity was also high with respect to depression (Calgary Depression Scale for Schizophrenia; CDSS; $r(33) = 0.08$) and positive symptoms (Positive and Negative Syndrome Scale; PANSS positive, $r(33) = 0.07$).

Table S1. Subscales and items of the BNSS and its two-factor structure.[1]

Subscale	Items	Two-factor structure
Anhedonia	(1) Intensity of pleasure during activities (2) Frequency of pleasurable activities (3) Intensity of expected pleasure from future activities	*Apathy*
Asociality	(5) Asociality: behavior (6) Asociality: internal experience	
Avolition	(7) Avolition: behavior (8) Avolition: internal experience	
Lack of normal distress	(4) Distress	*Diminished expression*
Blunted affect	(9) Facial expression (10) Vocal expression (11) Expressive gestures	
Alogia	(12) Quantity of speech (13) Spontaneous elaboration	

Note: The apathy factor includes asociality and avolition, terms that closely align with the typical use of the term apathy,[2] and also anhedonia. We decided to include the anhedonia subscale within our apathy factor for two reasons: first, two factor analytic studies of the authors of the BNSS assigned the same factor to these subscales.[1, 3] Second, the interview-based measure of anhedonia does not asses in-the-moment experience of pleasure in the narrow sense,[4] but rather taps into aspects that are strongly connected to motivation and goal-directed behavior (especially items 2 and 3).

Table S2. Correlations between the relative subjective values (SV) at each effort level and covariates.

		SV40	SV60	SV80	SV100
Psychopathology					
BNSS apathy		-0.37*	-0.58**	-0.69***	-0.44*
BNSS diminished expression		-0.10	-0.12	-0.12	-0.14
SANS apathy[a]		-0.35	-0.51**	-0.54**	-0.33
SANS diminished expression[a]		-0.14	-0.15	-0.12	-0.13
PANSS positive factor[b]		-0.15	-0.19	-0.24	-0.31
PANSS negative factor[b]		-0.23	-0.17	-0.24	-0.21
GAF		0.33	0.45*	0.46**	0.41*
PSP (total)		0.33	0.52**	0.58**	0.38*
CDSS (total)		-0.32[d]	-0.17[d]	-0.04[d]	0.26[d]
Number of hospitalizations		-0.004[d]	0.10[d]	0.002[d]	-0.23[d]
Chlorpromazine equivalents (mg/day)		-0.29	-0.28	0.07	0.14
Cognition[c]					
Composite cognitive ability	SZ	0.04	0.06	-0.03	0.03
	HC	*-0.36*	*-0.23*	*0.19*	*0.29*
Income	SZ	-0.16[d]	0.17[d]	0.06[d]	0.04[d]
	HC	*0.08*	*-0.21*	*-0.10*	*0.21*
Maximum Voluntary Contraction (MVC)	SZ	-0.12	-0.22	-0.33	-0.27
	HC	*0.07*	*-0.21*	*-0.10*	*0.21*
Anticipatory reward pleasure (VAS)	SZ	0.50**	0.43*	0.29	0.09
	HC	*-0.58***	*-0.35*	*-0.02*	*-0.12*
Perceived effort (overall, VAS)	SZ	-0.33	-0.26	-0.09	-0.26
	HC	*-0.09*	*-0.01*	*0.14*	*-0.02*

Note: * $p < .05$, ** $p < .01$, *** $p < 0.001$
Abbreviations: BNSS: Brief Negative Symptom Scale; SANS: Scale for the Assessment of Negative Symptoms; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; PSP: Personal and Social Performance Scale; CDSS: Calgary Depression Scale for Schizophrenia; SZ: Schizophrenia patient group; VAS: Visual Analogue Scale.
[a]*Apathy* = Avolition/Apathy, Anhedonia/Asociality ; *diminished expression* = Affective Flattening or Blunting, Alogia
[b]*Positive factor* = P1, P3, P5, G9; *negative factor* = N1, N2, N3, N4, N6, G7
[c]Cognition data has been z-transformed based on the data of the HC group for each test separately. The composite cognitive ability score was computed as the mean of the z-transformed test scores on subject level.
[d]Spearman correlations (r_s).

Fig. S1. Mean choice data for the different effort (40, 60, 80, and 100% MVC) and reward (1.5, 2, 2.5, 3, and 5 CHF) pairings for the HC group (A), the total patient group (B), the LOW-APATHY patients (C), and the HIGH-APATHY patients (D). Please note that additional iterative trials are not included in these figures. Error bars represent standard error of the mean.

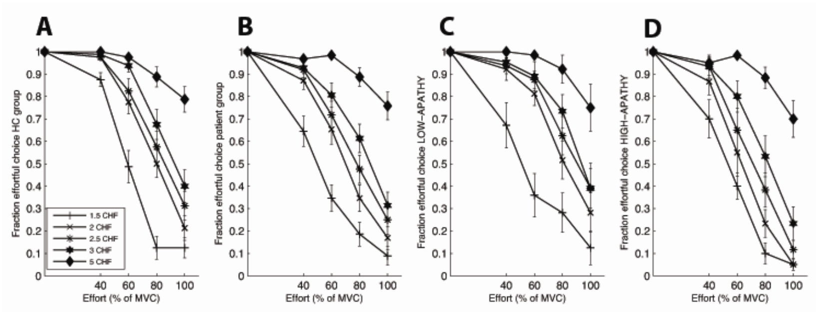
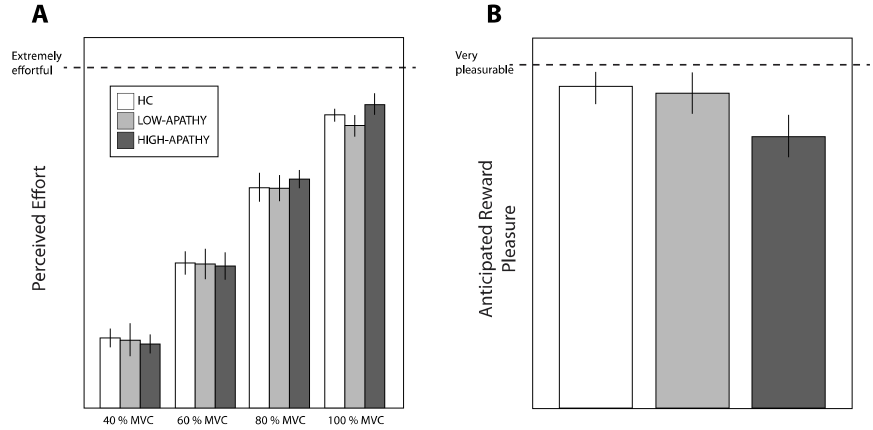


Fig. S2. (A) Perceived Effort of the 40, 60, 80, and 100 % effort levels and anticipated reward pleasure (B) in the healthy control (HC, white bars), the LOW-APATHY (light grey) and HIGH-APATHY (dark grey) group. Neither perceived effort ($F(2,48) = 0.08$, $p = 0.92$), nor anticipated reward pleasure was significantly different between groups ($F(2,48) = 1.55$, $p = 0.22$). Error bars represent standard error of the mean.



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Appendix C: Paper 3

"Apathy in Schizophrenia as a Deficit in the Generation of Options for Action".

This is a pre-copy-editing, author-produced PDF of an article under review at the *Journal of Abnormal Psychology* (Hartmann, M. N., Kluge, A., Kalis, A., Mojzisch, A., Tobler, P. N., Kaiser., under review. Apathy in schizophrenia as a deficit in the generation of options for action. *Journal of Abnormal Psychology*).

Manuscript

Apathy in Schizophrenia as a Deficit in the Generation of Options for Action

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Abstract

Apathy is a core negative symptom of schizophrenia and closely linked to functional outcome. However, knowledge about its mechanisms and its relation to decision-making is limited. In the present study, we examined whether apathy in schizophrenia is associated with "predecisional" deficits, that is, deficits in the generation of options for action. We applied verbal protocol analysis to investigate the quantity of options generated in ill-structured real world scenarios in 30 patients with schizophrenia or schizoaffective disorder and 21 healthy control participants. Clinical apathy ratings in patients correlated negatively with the quantity of generated options independent of other relevant clinical and cognitive measures. The present study provides empirical support for dysfunctional option generation as a possible mechanism for apathy. Our data emphasize the potential importance of "predecisional" stages in the development of apathy in schizophrenia and other neuropsychiatric disorders and might also inform the development of novel treatment options in the realm of cognitive remediation.

Keywords: schizophrenia, negative symptoms, option generation, decision-making, cognitive effort

Apathy in Schizophrenia as a Deficit in the Generation of Options for Action

Apathy or avolition is a core feature of schizophrenia (Kraepelin, 1919) and has recently been identified as one of the two dimensions of negative symptoms together with diminished expression (Blanchard & Cohen, 2006; Foussias & Remington, 2010; Messinger et al., 2011). Despite its unequivocal link to everyday functioning and outcome (Faerden et al., 2009; Fervaha, Foussias, Agid, & Remington, 2013; Kiang, Christensen, Remington, & Kapur, 2003), treatment options for apathy in schizophrenia remain scarce (Erhart, Marder, & Carpenter, 2006; Stahl & Buckley, 2007).

Empirically, apathy can be defined as a quantitative reduction in goal-directed behavior (Brown & Pluck, 2000; Levy & Dubois, 2006). Recent research has attempted to explain this reduction in goal-directed behavior with dysfunctional decision-making (Fervaha, Graff-Guerrero, et al., 2013; Hartmann et al., in press; Heerey, Bell-Warren, & Gold, 2008). These approaches, including our own, have mainly conceptualized decision-making as the evaluation and selection of options for action (Ernst & Paulus, 2005; Heckhausen, 1991). Critically, these approaches presuppose that options are already at hand, which however is rarely the case in real world decision situations (e.g., decision on what to do on a Sunday afternoon). To address this issue, it has been proposed that models of decision-making should be complemented by a "predecisional" stage, in which options for actions have to be generated before they can be decided on (Fellows, 2004; Kalis, Kaiser, & Mojzisch, 2013; Kalis, Mojzisch, Schweizer, & Kaiser, 2008; Smaldino & Richerson, 2012). Such integrative theoretical frameworks also hypothesize that apathy could in part be due to dysfunctional option generation (Fellows, 2004; Kalis et al., 2008; Sinha, Manohar, & Husain, 2013; Smaldino & Richerson, 2012). However, to our knowledge this has not yet been empirically tested with regard to apathy in neuropsychiatric disorders.

Based on these theoretical frameworks we hypothesized that apathy would be negatively correlated with the quantity of generated options for action. To test this main hypothesis we applied verbal protocol analysis to obtain a quantitative measure of options generated in ill-structured real-world scenarios. To assess option generation in a broad approach and to test secondary hypotheses, we applied a 2 × 2 factorial design. (1) We manipulated the "stopping-rule" in the option generation phase, that is, participants either decided on their own when enough options were generated to initiate satisfactory goal-directed action or they were encouraged to generated a maximum number of options. (2) We further designed half of the scenarios as situations with an implicit goal state (problem-solving scenarios) and the other half as scenarios without such (open scenarios). Our secondary hypotheses were that the association of apathy with quantity of generated options would be more pronounced in the scenarios with a subjective stopping rule relative to the maximum condition and in the open scenarios relative to problem-solving scenarios.

Methods

Participants

Thirty patients meeting DSM-IV (APA, 2000) criteria for schizophrenia (n = 24) or schizoaffective disorder (n = 6, no mood episode) and 21 healthy control (HC) participants took part in the present study. The local Ethics committee approved the study and all participants gave written informed consent. Patients were clinically and pharmacologically stable inpatients at the end of their hospitalization (n = 25) or outpatients (n = 5) treated at the Psychiatric Hospital of the University of Zurich. Please note that the average inpatient stay for patients with schizophrenia in Swiss psychiatric hospitals is above 40 days (BFS, 2012), therefore many of our inpatients would be treated as outpatients in other health care systems. Importantly, inpatients participated in a multimodal treatment program and were encouraged to engage in activities outside the hospital. Thus, they had the opportunity for a broad range of activities allowing appropriate assessment of negative symptoms. Patients were excluded if (1) daily *lorazepam* dosage exceeded 1 mg, (2) if florid positive symptoms were present (Positive and Negative Syndrome Scale; PANSS (Kay, Fiszbein, & Opler, 1987); any positive subscale item score > 4), or (3) if additional DSM-IV axis I or axis II diagnostic criteria were met (according to treating clinician). To confirm axis I diagnosis in patients, exclude comorbid axis I disorders and ensure the absence of axis I disorders in the HC group we employed the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998).

Clinical Rating Scales

For the psychopathological characterization of the patient sample the following instruments were used: Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011), PANSS, Personal and Social Performance Scale (PSP; Schaub & Juckel, 2011) and the Calgary Depression Scale for Schizophrenia (CDSS; Addington, Addington, & Schissel, 1990). The BNSS was translated to German by the senior author. A BNSS-naïve native English speaker and attending psychiatrist performed the back-translation. The scores for the two critical negative symptom factors in the BNSS – apathy and diminished expression - were calculated according to the two-factor structure proposed by the authors of the scale (Kirkpatrick et al., 2011; Strauss et al., 2012).

Cognitive Assessment

We assessed cognitive ability for inclusion as a possible confound in our study. Based on our previous research on the cognitive basis of option generation (Kaiser et al., 2013), we included a verbal memory measure (VLMT; German version of the Auditory Verbal Learning Memory Test; Helmstaedter, Lendt, & Lux, 2001), and semantic and phonemic fluency (animal naming, s-words; Delis, Kaplan, & Kramer, 2001). We also assessed processing speed (Digit-Symbol Coding; Von Aster, Neubauer, & Horn, 2006), verbal crystallized intelligence (MWT-B; Lehrl, 1999), and creativity (number of creative items on the brick item of the Alternate Uses Test; Guilford, 1967). Each test score was z-transformed based on HC group data.

Option Generation Task

In the option generation task, participants were verbally presented with 20 ill-structured short real-world scenarios for which they had to verbally generate options for action (task adapted from Kaiser et al., 2013). Our experiment was designed as a 2 (subjective stopping rule vs. maximum) × 2 (problem solving vs. open scenarios) within-subjects factorial design with five scenarios for each cell.

In the first half of the experiment (10 scenarios), participants were instructed to generate options until they felt confident that they could satisfactorily decide on an option for action (subjective stopping rule). In the second half of the presented scenarios (10 scenarios), participants were instructed to generate as many subjective options as they could think of (maximum). When participants stopped generating options, they were prompted twice to think of additional options. However, if generation time per scenario exceeded two minutes the experimenter stopped the participant and proceeded with the next scenario.

As a second factor, scenarios were either designed as ill-structured problem-solving scenarios with an implicit desired outcome (e.g., “You are alone in an elevator when it suddenly gets stuck. What could you do?”), or ill-structured “open” scenarios that did not imply any course of action or goal state (e.g., “It’s a beautiful Sunday. What could you do?”). The second factor was pseudo-randomly manipulated within the two blocks of 10 scenarios each.

Data Processing

Generated options were recorded and later transcribed to spreadsheet software for further analyses. For the statistical analyses only the options were included that clearly entailed goal-directed behavior (e.g., “Go to the movies with friends.”). In contrast, options that were not goal-directed (e.g., “Wait and see what happens.”) or redundant with respect to an already generated option (i.e., congruent in terms of associated behavior) were excluded from these analyses.

Statistical Analyses

Potential differences in demographic, clinical, and cognitive measures as well as task performance were assessed using two-sample *t*-tests for continuous and chi-square tests for categorical variables. Degrees of freedom were adjusted if inequality of variance had to be assumed according to Levene’s tests.

To test our main hypothesis, we computed Pearson correlation coefficients (*r*) between apathy and overall mean quantity of generated options. A partial correlation was then computed between apathy and overall quantity of generated options, holding constant or controlling for clinical and cognitive characteristics. To test our secondary hypotheses, we computed additional correlations between apathy and mean quantity of generated options in each factor separately and computed pairwise *t*-statistics (Chen & Popovich, 2002) to investigate how each factor impacted the strength of correlation (subjective stopping rule vs. maximum; problem-solving scenarios vs. open scenarios) .

To investigate the pure effect of the experimental manipulation on the quantity of options generated and to explore potential differences between healthy controls and patients, we conducted a 2 (subjective stopping rule vs. maximum) × 2 (problem-solving vs. open scenario) × 2 (HC vs. patient group) repeated measures analysis of variance (ANOVA). Post hoc pairwise comparisons were conducted to explore specific differences.

Statistical tests report two-sided *p*-values and were computed with SPSS version 22 (IBM Corp., Armonk, NY).

Results

Sample Characteristics

Demographic, clinical, and cognitive characteristics and group comparisons thereof are reported in Table 1.

Correlational Analyses

We observed a strong negative correlation between apathy and overall mean number of generated options, $r(28) = -.68$, $p < .001$ (Figure 1). In other words, apathy was associated with a reduced quantity of generated options. Of note, the diminished expression factor of the BNSS was also significantly correlated with overall mean number of generated options, $r(28) = -.40$, $p = .03$ A partial correlation was then computed between apathy and overall mean number of generated options, controlling for relevant clinical (CPZ equivalents, BNSS diminished expression, PANSS positive, CDSS depression) and cognitive variables (all tests see Cognitive Assessment). The result indicates a strong relation between apathy and overall mean quantity of generated options even when controlling for these covariates, $r(18) = -.67$, $p = .001$. Please note that if any of the covariates were the principal determinant of quantity of options generated this partial correlation should not be significant.

Correlation coefficients of apathy with mean generated options in the four within-subject conditions were all highly significant, subjective stopping rule: $r(28) = -.61$, maximum: $r(28) = -.66$; problem-solving scenarios: $r(28) = -.71$, open scenarios: $r(28) = -.61$, all *p*s < .001. However, pairwise comparisons of the correlations in each of the two factors were non-significant (all *p*s > .05) according to a *t*-statistic (Chen & Popovich, 2002).

Further correlational analyses revealed no significant association of apathy with option generation time, that is, how long they took on average to generate options, $r(28) = -.21$, $p = .26$, but a significant correlation with frequency of generated options, $r(28) = -.45$, $p = .01$.

Group analyses

To investigate overall effects of the experimental manipulation and at the same time compare the HC to the patient group, we conducted a 2 × 2 × 2 repeated measures ANOVA (Figure 2). There was a significant main effect of group, $F(1, 49) = 40.91$, $p < .001$, indicating that healthy controls generated more options than patients ($M_{HC} = 5.87$, $SD_{HC} = 1.58$; $M_{patients} = 3.54$, $SD_{patients} = 1.03$). The main effect of the factor "subjective stopping rule vs. maximum" was also significant, $F(1, 49) = 121.81$, $p < .001$, indicating that more options were generated in the maximum condition compared to when subjects terminated option generation on subjective grounds. We also found a significant main effect of the factor "problem-solving vs. open", $F(1, 49) = 64.00$, $p < .001$, indicating that more options were generated in the open compared to problem-solving scenarios. There was further a significant two-way interaction between the two experimental factors "subjective stopping rule vs. maximum" and "problem-solving vs. open", $F(1, 49) = 43.92$, $p < .001$. Moreover, we found an interaction between group and "subjective stopping rule vs. maximum", $F(1, 49) = 44.31$, $p < .001$. This interaction effect reflects the fact that groups differentially increased the quantity of generated options due to encouragement in the maximum condition (HC > patients). We also found a two-way interaction between group and "problem-solving vs. open", $F(1, 49) = 8.95$, $p = .004$, indicating that the HC group increased the quantity of generated options in problem-solving relative to open scenarios more strongly than patients. Finally, also the three-way interaction was significant, $F(2, 48) = 4.37$, $p = .02$, reflecting the fact that group differences were most pronounced in the factor combination maximum/open. Follow up pairwise comparisons revealed that the HC group generated more options than patients in all factor combinations (*p*s < .001; Figure 2).

The patient group did not differ significantly from the HC group in the mean time taken to generate options averaged over all scenarios, $t(23.22) = 0.64$, $p = .53$, but generated significantly less options per second, $t(20.01) = 2.86$, $p = .01$.

Discussion

Apathy in schizophrenia can be conceptualized as a disorder of decision-making and goal-directed behavior (Brown & Pluck, 2000; Hartmann et al., in press). In the present study, we hypothesized that apathy is partially due to "predecisional" deficits, that is, deficits in the generation of options for action in ill-structured real world scenarios. We found a very strong correlation of apathy with the quantity of generated options. Importantly, this association is not driven by diminished expression (including alogia), medication, positive or depressive symptoms and global cognitive impairment. Thus, these data suggest a potentially important role of option generation as a specific "predecisional" cognitive mechanism contributing to apathetic states in schizophrenia.

In the current study, we experimentally manipulated two factors - the stopping rule (subjective stopping rule vs. maximum) and the type of scenario (problem-solving vs. open). Pairwise comparisons showed that neither the stopping rule, nor the type of scenario did significantly affect the correlation of apathy with quantity. However, all correlation coefficients were strongly negative, emphasizing that apathy seems to be linked to deficient generation of options in various contexts. Thus, our secondary hypotheses – a stronger association of apathy with quantity of generated options when subjective stopping rule as compared to maximum applied and in open compared to problem-solving scenarios – could not be confirmed in this study.

Group differences were significant in all conditions (HC > patients), however they were more pronounced in the maximum condition compared to when subjects were free to stop and in open relative to problem-solving scenarios. In other words, our experimental manipulation of stopping-rule and type of scenario impacted option generation more strongly in healthy controls compared to patients. The differential effect of stopping-rule might either be explained by a genuinely smaller repertoire of options for action in patients or a failure to motivate further option generation due to a social prompt (i.e., the maximum condition). The differential effect of type of scenario on the other hand is consistent with clinical observations that schizophrenia patients seem to be most strongly affected in open situations where behavior has to be initiated to satisfy personal goals and motives. One could speculate, that this reflects an inability to generate more options as the hypothetical “option space” widens (problem-solving vs. open). In sum, patients did not adjust the amount of options generated as strongly as healthy control in response to experimental manipulations.

It has been proposed that apathy in neuropsychiatric patients can be divided into three subtypes of disrupted processing: motivational (linking emotional-affective signals with behavior), cognitive, and auto-activation (Levy & Dubois, 2006). While auto-activation deficits are primarily observed in patients with basal ganglia lesions, compelling evidence points to motivational deficits in schizophrenia patients with apathy (for a recent review see Strauss, Waltz, & Gold, 2014). In contrast, option generation is a cognitive process occurring in a “predecisional” stage. The role of cognitive dysfunction in the pathogenesis of apathy in schizophrenia remains a matter of debate. Cognitive domains commonly associated with apathy are processing speed, verbal fluency, verbal memory, and working memory (e.g., Berman et al., 1997; Bozikas, Kosmidis, Kioperlidou, & Karavatos, 2004; O'Leary et al., 2000). However, their relationship seems to be moderate at the most requiring meta-analytic approaches to achieve required power (Dibben, Rice, Laws, & McKenna, 2009; Heinrichs & Zakzanis, 1998; Keefe et al., 2006). One possible explanation for this pattern might be that prior research has not specifically investigated cognitive processes that are directly linked to everyday decision-making and goal-directed behavior (Levy & Dubois, 2006). In contrast to the moderate associations of apathy with cognition in previous studies, we found a strong correlation of apathy with quantity of generated options in our task involving ill-structured everyday scenarios. The observed quantitative reduction in generated options strongly suggests an important role for specific cognitive processes in the development of cognitive apathy in schizophrenia.

In addition to framing deficient option generation as a cognitive deficit, one could also view the present findings as a motivational deficit as mentioned above. In particular, they are in line with previously reported dysfunctional cost-benefit decision-making in schizophrenia (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013; Hartmann et al., in press). When generating options for action the agent has to dynamically weigh the potential increase in future reward that might come with additional options against the cost of time and cognitive effort that have to be invested in the generation process. Thus, one should stop to generate options when expected costs outweigh expected benefits (Gigerenzer & Todd, 1999). There is evidence for degraded reward value representations (Gold, Waltz, Prentice, Morris, & Heerey, 2008) and overweighing of time (Heerey, Robinson, McMahon, & Gold, 2007) and effort costs (Gorissen, Sanz, & Schmand, 2005; Hartmann et al., in press) in decisions of patients with schizophrenia. It is therefore possible to approach the quantitative reduction in option generation from the viewpoint of dysfunctional cost-benefit decision-making, that is, the effort of generating new options is overweighted in relation to their potential benefits.

In the present study, we assumed that if an agent generates more options, the decision outcome would be better and should lead to an increase in goal-directed behavior. This is in line with the classical notion that a complete "option space" or "option tree" is beneficial for optimal decision-making in complex situations (Adelman, 1987; Gettys, Pliske, Manning, & Casey, 1987; Keller & Ho, 1988). More recently, some authors (Klein, Wolf, Militello, & Zsambok, 1995; Raab & Johnson, 2007) have suggested that in constrained situations highly trained experts (e.g., athletes and chess players) need not extensively generate and evaluate options for a satisfactory outcome because their first ones are usually the best ("take-the first-heuristic", "less-is-more"). However, our premise is in general agreement with recent studies on option generation in non-clinical populations, which have applied less structured scenarios (Ward, Suss, Eccles, Williams, & Harris, 2011; Ward, Torof, Whyte, Eccles, & Harris, 2010). It is thus conceivable that highly automated expert decisions differ qualitatively from decision situations people face in everyday ill-structured environments, the latter requiring more options to arrive at optimal decisions.

In our study we have employed scenarios with very few constraints in order to emulate real-world situations. In these situations apathetic patients show a decreased quantity of generated options.. However, a consequence of employing real-world scenarios is that assessment of option quality is rendered highly problematic. Since our scenarios did not contain an optimal or near optimal solution, quality assessment was not possible. An alternative to task-based assessment is the interview-based assessment of real-world problem-solving skills, which have been shown to be negatively associated with negative symptoms in schizophrenia (Revheim et al., 2006).

A few limitations of the present study should be addressed. First, sample size was rather modest. However, our main results are robust and should be replicable in a larger sample. Second, our study design is correlational and therefore does not allow to make causal statements. One explanation of our data could be that disease specific pathophysiological mechanisms lead to deficits in option generation, which then cause a reduction in goal-directed behavior (i.e., apathy). However, one could also speculate that deficits in option generation reflect the fact that apathetic individuals have experienced less variance in behavior in specific decision situations (due to an underlying disease mechanism) and thus cannot retrieve as many options for action from long-term memory. Importantly, regardless of not yet clarified causality the current study adds to the growing knowledge of apathetic phenomena.

From a more practical perspective, we believe that our findings have potential clinical implications. For example, the training of option generation could be implemented in a combined cognitive remediation (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011) and psychotherapy setting (Drake et al., 2013). Patients could, for instance, be trained in a computerized option generation task while transfer to everyday life would be targeted in therapy sessions. Future studies could test the applicability and efficacy of such option generation trainings in clinical settings. Independent of this, the current study provides empirical support for the potential importance of “predecisional” stages in decision-making for the development of neuropsychiatric symptoms, particularly apathy.

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Table 1

Demographic and clinical characteristics and cognitive test scores

	Healthy controls (n = 21)	Patient group (n = 30)	p-value (t/χ^2)
Demographics			
Age (years)	32.33 (6.70)	30.33 (8.47)	0.37
Gender (male/female)	16/5	23/7	0.97
Handedness (r/l)	17/4	28/2	0.18
Education (years)[a]	12.55 (3.98)	9.98 (1.65)	**< 0.01**
Clinical variables			
CPZ equivalents[b]	-	563.83 (419.56)	-
Duration of illness (years)	-	9.74 (8.06)	-
BNSS apathy[c]	-	15.77 (6.16)	-
BNSS diminished expression[c]	-	10.23 (6.46)	-
PANSS positive[d]	-	7.00 (2.80)	-
PANSS negative[d]	-	13.83 (4.76)	-
PSP scale	-	54.07 (10.13)	-
CDSS	-	2.27 (2.29)	-
Cognitive test scores[e]			
Verbal memory (delayed recall)	0 (1)	0.15 (1.50)	0.69
Processing speed	0 (1)	-1.29 (0.89)	**< 0.001**
Phonemic fluency	0 (1)	-0.84 (0.88)	**< 0.01**
Semantic fluency	0 (1)	-1.45 (0.89)	**< 0.001**
Crystallized verbal intelligence	0 (1)	-1.19 (1.69)	**< 0.01**
Creativity	0 (1)	-0.44 (0.69)	0.07

Note. Data are presented as means and standard deviations. *Abbreviations:* CPZ: Chlorpromazine; BNSS: Brief Negative Symptom Scale; PANSS: Positive and Negative Syndrome Scale; PSP: Personal and Social Performance; CDSS: Calgary Depression Scale for Schizophrenia. [a]Compulsory education in Switzerland is 9 years. [b]All patients were receiving atypical antipsychotics at the time of testing. Two individuals were additionally medicated with low doses of typical antipsychotics. 6 were receiving an SSRI, 3 were receiving low doses of benzodiazepine, 1 was receiving a mood stabiliser, 2 were receiving zolpidem against insomnia. [c]*Apathy* = Avolition/Apathy, Anhedonia/Asociality ; *diminished expression* = Affective Flattening or Blunting, Alogia. [d]*Positive factor* = P1, P3, P5, G9; *negative factor* = N1, N2, N3, N4, N6, G7. [e]Cognition data has been z-transformed based on the data of the HC group for each test separately.

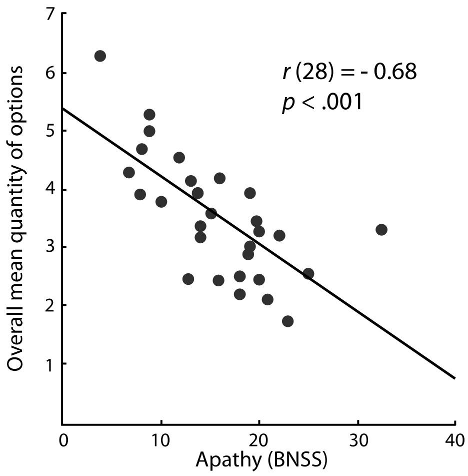

Figure 1. Scatterplot and correlation coefficient between apathy and mean quantity of generated options across all 20 scenarios.

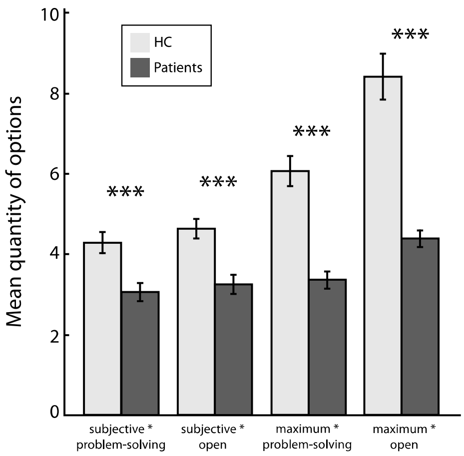

Figure 2. Mean quantity of generated options in the four conditions in the healthy control group (HC) and the patient group. Error bars represent standard error of the mean. *** = $p < .001$.

Appendix D: Curriculum Vitae

Personal Data

Name	Matthias Hartmann (-Riemer)
Date of birth	March 14, 1985
Place of birth	Zurich (Switzerland)
Nationality	Swiss

Education

2011 – 22.10.2014	University of Zurich; Faculty of Economics, Business Administration and Information Technology; Doctoral studies in Neuroeconomics
2004 – 2011	University of Zurich; Faculty of Arts; Institute of Psychology: Master of Science (M. sc.) in Clinical Psychology (Minors: Biology, Psychopathology)
1999 – 2003	Kantonsschule Hottingen, Matura (Economy & Law)